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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ervebo

Common name: Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live)

Procedure No. EMEA/H/C/004554/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AS/ BAS	Active substance/also referred to as the bulk active substance
BDS	Bulk drug substance
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CCCs	Contacts and contacts of contacts
CCI	Container closure integrity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Conditional Marketing Authorisation
CPP	Critical process parameters
CQA	Critical quality attributes
CSR	Clinical Study Report
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
EBOV	Ebolavirus
EEA	European Economic Area
ELLI	Eurofins Lancaster Laboratories, Inc.
EMA	European Medicines Agency
EVA	Ethylene vinyl acetate copolymer
EVD	Ebola virus disease
EVOH	Ethyl vinyl alcohol
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFB	Final formulated bulk
FP	Finished product
G/GP	Glycoprotein

GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practice
GMT	Geometric mean titre
GP	Glycoprotein
GP-ELISA	Glycoprotein enzyme-linked immunosorbent assay
HCP	Host cell proteins
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
ICH	International Committee on Harmonization
IgG	Immunoglobulin G
IPC	In-process control
MCB	Master cell bank
MIA	Manufacturing and Importation Authorisation
MO	Major objection
MVS	Master virus seed
NHP	Non-human primate
OMCL	Official Medicines Control Laboratory
PCR	Polymerase chain reaction
PCV	Porcine circovirus
pfu	Plaque Forming Unit
PHEIC	Public Health Emergency of International Concern
Ph. Eur.	European Pharmacopeia
PP	Per-protocol
PPQ	Process performance qualification
PRIME	(European Medicines Agency's) Priority Medicines
PRNT	Plaque reduction neutralization test
PsvNA	Pseudovirion neutralization assay
PV/ PPQ	Process validation/ also known as process performance qualification
QC	Quality control
RB	Roller bottle
rHSA	Recombinant human serum albumin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase-polymerase chain reaction

rVSV	Recombinant vesicular stomatitis virus
rVSVΔG-ZEBOV-GP	Ebola Zaire vaccine
SA	Scientific Advice
SAE	Serious adverse event
SEC-HPLC	Size-exclusion HPLC
sGP	Shed GP
SO	Specific objection
TEAEs	Treatment emergent adverse events
TOR	Time-out-of-refrigeration
UFP	Ultrafiltered product
WCB	Working cell bank
WHO	World Health Organization
WVS	Working virus seed
ZEBOV	Zaire Ebola virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 11 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Ervebo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2016.

The applicant applied for the following indication: "Ervebo is indicated for active immunization of at-risk individuals 18 years of age and older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus. See sections 4.4 and 5.1 for important information on the data that support this indication".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, quality data, complete non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0095/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0095/2017 was not yet completed as some measures were deferred.

Applicant's requests for consideration

Conditional marketing authorisation

During the assessment certain limitations with regards to the comprehensiveness of the available pharmaceutical data were identified, therefore in light of the emergency situation a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004 was considered.

Accelerated Assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance recombinant Vesicular Stomatitis Virus strain Indiana with a deletion of the VSV envelope glycoprotein replaced with the Zaire Ebola Virus Kikwit 1995 strain surface glycoprotein contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME support

Ervebo was granted eligibility to PRIME on 23 June 2016 in the following indication: Active immunization of at-risk individuals 18 years and older in reactive use situations to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.

Eligibility to PRIME was granted at the time based on the following:

- In view of the very high case-fatality rate of EVD and of the fact that no approved method to prevent or treat EVD currently exists, it was agreed that prevention of EVD is currently an unmet medical need.
- Based on the presented data (supportive non-clinical profile, antibody response to the product shown by ELISA and virus neutralization assays in phase 1 studies, interim analysis of the phase 3 ring vaccination trial, preliminary safety data collected in the clinical studies conducted to date), CHMP agreed that V920 has the potential to address the identified unmet need.
- Despite the late stage of development, additional discussions between the EU regulators and WHO are foreseen (e.g. in the area of clinical trial design for future outbreaks, aspects regarding correlates of protection, immunobridging).

Upon granting of eligibility to PRIME, the Rapporteur was appointed by the CHMP.

A kick-off meeting was subsequently organised with the EMA, Rapporteur and assessors from relevant scientific committees. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: limitations in the manufacturing process, clarification needed for assay validation and immunogenicity data (including correlation of protection), clarification on proposed indication wording and pre/post-exposure prophylaxis, long-term duration of efficacy, studies in special populations, paediatric investigation plan, risk management plan and planning of post-authorisation submissions.

Scientific advice

The applicant received Scientific Advice from the CHMP on 23 April 2015 (EMEA/H/SA/3078/1/2015/III) and 24 September 2015 (EMEA/H/SA/3078/1/FU/1/2015/III). These were rapid advices in the context of the 2014-2016 Ebola outbreak. The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Starting material
- Assay validation and PPQ data
- Analytical comparability to support changes in manufacturing
- Stability studies
- Minimum quality requirements in case of an urgent need of the vaccine
- Toxicology, nonclinical pharmacology and bio-distribution studies
- Environmental risk assessment
- Minimum non-clinical requirements in case of an urgent need of the vaccine
- Pathways for licensure to enable timely availability of the vaccine in the affected communities
- Safety database, studies in children and in HIV+ subjects

- Provision of data on a rolling basis during review, as well as submission of some of the trials as post-marketing commitments.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bart Van der Schueren Co-Rapporteur: Jan Mueller-Berghaus

Accelerated Assessment procedure was agreed-upon by CHMP on	31 January 2019
The application was received by the EMA on	11 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	29 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	29 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 June 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 June 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2019
The following GMP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one site for quality control of the finished product in USA between 11 and 12 December 2019. The outcome of the inspection carried out was issued on	6 February 2019
– A GMP inspection at one site for biostorage in USA between 19 and 20 February 2019. The outcome of the inspection carried out was issued on	28 February 2019
– A GMP inspection at one site for the manufacture of cell banks in USA between 19 and 22 March 2019. The outcome of the inspection carried out was issued on	13 June 2019
– A GMP inspection at one site for quality control of the finished product and of the active substance in USA between 17 and 21 June	6 September 2019

<p>2019. The outcome of the inspection carried out was issued on</p> <ul style="list-style-type: none"> – GMP inspections at four sites for quality control testing for the manufacture of finished product and active ingredient in USA between 27 and 31 May 2019. The outcome of the inspection carried out was issued on – A GMP inspection at one site for quality control of the active substance in USA between 10 and 12 September 2019. The outcome of the inspection carried out was issued on 	<p>26 September 2019</p> <p>26 September 2019</p>
<p>The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on</p>	<p>06 September 2019</p>
<p>The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on</p>	<p>17 September 2019</p>
<p>The applicant submitted the responses to the CHMP List of Outstanding Issues on</p>	<p>24 September 2019</p>
<p>The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on</p>	<p>03 October 2019</p>
<p>The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ervebo on</p>	<p>17 October 2019</p>

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ebola virus disease (EVD) is a serious illness that originated in Africa. The first Ebola disease outbreaks were reported back in 1976. Since then more than 30 outbreaks have occurred in Africa with more than 30,000 people affected by the disease and almost 15,000 deaths. The first EVD outbreaks occurred in remote villages in Central Africa, near tropical rainforests. The 2014–2016 outbreak in West Africa involved major urban areas as well as rural ones and was declared a public health emergency of international concern (PHEIC) by WHO. The causative agent of the disease is the Ebola virus, a negative-stranded RNA virus belonging to the *Filoviridae* family. Ebola virus infection causes an acute often serious illness with variable -but usually high- case fatality rate. The average EVD case fatality rate is around 50% but rates have varied from 25% to 90% in past outbreaks depending on the virus species involved. The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.

On 01 August 2018 the Ministry of Health of the Democratic Republic of the Congo (DRC) declared a new outbreak of EVD in North Kivu Province, which is currently ongoing. As of 17 October 2019, 3,228 cases of disease have been reported with a death toll of 2,157 cases.

2.1.2. Epidemiology

Since the initial identification of Ebola viruses in 1976, more than 20 outbreaks of Ebola disease have been reported in sub-Saharan Africa, mostly in Sudan, Uganda, Democratic Republic of Congo and Gabon. Most of these outbreaks have occurred in isolated rural areas, but the outbreak in Gulu in 2000 was in a semi-urban area of Uganda. It is conceivable that smaller outbreaks might not have been detected. The largest Ebola outbreak to date occurred in 2014–16 in West Africa, predominantly affecting both rural and urban areas in Guinea, Sierra Leone, and Liberia with very high incidence and mortality (>28 000 cases with >11 000 deaths). Due to potential under-reporting the true burden of disease might have been even higher. In this outbreak, the overall mean case fatality rate in confirmed cases with recorded clinical outcomes was 62.9%. The epidemic peaked in August through October 2014. In March 2016, the WHO declared the end of the Public Health Emergency of International Concern (PHEIC). Sierra Leone was declared free of Ebola transmission in March 2016. After a few sporadic cases in Liberia and Guinea in March/April 2016, these two countries were also declared free of Ebola transmission in June 2016.

During the evaluation procedure, the World Health Organization declared the ongoing outbreak in DRC a Public Health Emergency of International Concern.

So far EVD outbreaks have been restricted to African countries. However, there is a risk that the disease could spread to other continents due to e.g. international travel or secondary infection from patients coming from African countries (cases were reported in Spain and the US). Unfamiliarity with EVD outside of endemic areas can lead to delayed diagnosis of imported cases.

Beyond the direct morbidity and mortality due to EVD, large outbreaks of the disease have indirect effects on population health based on the diversion of resources from programmes aimed at controlling other diseases of major importance.

Ebola virus disease is not an airborne disease and only symptomatic patients are contagious. As transmission requires direct contact with bodily fluids, the risk of infection is considered very low if

precautions are strictly followed. The probability that EU/EEA citizens living in or travelling to EVD-affected areas of the DRC will be exposed to the virus is low, provided they adhere to the recommended precautionary measures. Nosocomial transmission can occur. Healthcare workers can be infected through close contact with infected patients. However, health worker infections are preventable, and the risk for infection can be significantly reduced through the appropriate use of infection control precautions and adequate barrier procedures.

A preventive vaccine for EVD could be used to protect individuals at high risk in advance of exposure and also to interrupt transmission during an epidemic. Since the monovalent V920 vaccine elicits rapid immunity after a single dose, it has the potential for use as prophylactic vaccine to protect against EVD caused by Ebola Zaire virus.

2.1.3. Aetiology and pathogenesis

Aetiology

Ebolaviruses (EBOV) belong to the genus *Ebolavirus* of the *Filoviridae* family in the order *Mononegavirales*. All members of this order possess a non-segmented, negative-sense RNA genome of 19 kb with seven open reading frames, which is encapsidated by the viral nucleoprotein (NP). The NP–RNA complex acts as the template for genome replication and assembles into a helical nucleocapsid (NC) along with accessory proteins. EBOV has a striking, filamentous structure of about 800 nm in length and 80 nm in diameter. The helical nucleocapsid acquires an envelope by budding from the plasma membrane. The viral envelope contains spikes consisting of the glycoprotein (GP) trimer. This GP molecule achieves the combined functions of attachment to host cells, endosomal entry, and membrane fusion.

The genus *Ebolavirus* of the *Filoviridae* family includes five species: Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus, and Zaire ebolavirus. Among them, the Zaire ebolavirus, usually called Ebola virus (EBOV), is the main causative agent of human Ebola virus disease (EVD) outbreaks. EBOV persists in the environment in a still unidentified animal reservoir, most likely fruit bats, which maintain the virus in an enzootic cycle. Human infection represents a sporadic event taking place in the context of a human-animal interface. Transmission is mainly due to contact with blood or body fluids from infected humans or animals.

Pathogenesis

The major route of infection is through the mucosa or skin from where the virus reaches macrophages, monocytes, and dendritic cells, leading to spread to regional lymph nodes, liver, and spleen. Macrophages and monocytes stimulated by EBOV release a “cytokine storm”, which in turn is responsible for damage to tissues and blood vessels. Death occurs due to blood loss and/or coagulation. Coagulopathy occurs due to thrombocytopenia, loss of anticoagulant protein C, destruction of clotting factors, and also due to destruction of fibrin. Damage to blood vessels causes disseminated intravascular coagulation as well as renal failure. Antibodies developed against EBOV bind with the complement C1q and reach the binding sites on dendritic cells and macrophages, leading to damage of these cells. Lesions related to EVD include extensive haemorrhages of the mucosa, necrosis of different organs like liver, kidney, testes, and ovaries. Necrotic foci with inflammatory cells can be found in hepatic lobules, and there may be multinucleated syncytia formation in the hepatic cells. Necrosis of red pulp and fibrin deposition are the characteristic lesions seen in the spleen. Gastrointestinal tract shows mononuclear infiltration into the submucosa and lamina propria. Mild emphysema, oedema in the terminal alveoli, and stasis of blood can be noticed in the lung parenchyma. It has also been shown that macrophages in the chambers of the eye, brain, and epididymis are sites of viral persistence (sanctuary sites).

2.1.4. Clinical presentation, diagnosis and stages/prognosis

Clinical presentation

Ebola disease is a viral haemorrhagic fever affecting humans and other primates that is caused by infection with ebolaviruses. Following an incubation period of 2–21 days, Ebola disease typically starts as a non-specific viral syndrome with abrupt onset. At this stage the most frequent symptoms are high fever, malaise, fatigue, and body aches (early febrile or mild stage, 0-3 days). These symptoms usually develop after a few days into gastrointestinal symptoms including nausea, vomiting, and diarrhoea (gastrointestinal involvement stage, 3-10 days). These manifestations can range from mild-to-severe, with body fluid loss of up to 5–10 L/day. Other, rarer, symptoms are cough and dyspnoea, conjunctival injection, hiccups, or localised pain of chest, abdomen, muscles, or joints.

Part of the patients may recover from this stage; others however will enter into deterioration of symptoms, ultimately going into shock, possibly due to hypovolaemia and a systemic inflammatory response. At this stage (complicated stage, 7-12 days), patients can present haemorrhagic events, such as conjunctival bleeding, petechiae, gastrointestinal bleeding, mucosal haemorrhage. Neurological events are rare and include confusion, delirium, and convulsions. Cases of Ebola disease-related encephalitis have been reported. Other late symptoms include dysphagia, throat pain, and oral ulcers. A maculopapular rash has been described. Exceptionally, sudden death can occur in recovering patients, possibly due to cardiac arrhythmias. If patients survive the stage of shock, gradual recovery can occur.

Irrespective of the severity of the acute disease, Ebola virus tends to persist, specifically in sites where immune response is less effective (e.g. the eye, central nervous system, and testis). Persistence is associated with clinical sequelae, disease reactivation, long-term virus shedding, and virus transmission. Virus found in the seminal fluid can still be infectious and be sexually transmitted for more than a year after disease onset. Cases of women transmitting the virus via breastfeeding have been reported, although the duration of infectivity by this route is unknown. Reports suggest that other reservoirs and other human-to-human transmission routes of persisting virus in humans could still be uncovered.

Laboratory features include variable degrees of anaemia and thrombocytopenia as well as changes in number and type of white blood cells. Renal dysfunction (in up to 50% of case) and substantial increases in liver enzymes are common. Likewise, creatine phosphokinase and amylase concentrations can be increased. Electrolyte abnormalities are common, especially hypokalaemia, hyponatraemia, and hypocalcaemia. Clotting tests can indicate a varying degree of intravascular coagulation. Metabolic acidosis can occur, particularly in cases of shock and renal failure.

High viral loads, combined with severe muscle breakdown and renal impairment, have consistently been predictive of death. Differences in severity of clinical events and outcome might exist between young children, young adults, and older people. Pregnant women face higher mortality and risk of miscarriage and stillbirth. Clinical presentation can be aggravated by concurrent comorbidities and infections, such as malaria and bacterial sepsis. Clinical signs and symptoms have varied across the different Ebola outbreaks reported during the last decades. This variation is at least partly due to the specific outbreak context and the ebolavirus species involved. For example, haemorrhagic events were highly prevalent in the 1976 outbreak in Yambuku, but less so in many other outbreaks, including the 2013-2016 West African one in which haemorrhage was uncommon. Furthermore, during the West African outbreak, fever was absent in at least 10% of the cases.

Diagnosis

Diagnosis of EVD on the basis of clinical symptoms can be difficult as clinical manifestations are similar to those of other infectious diseases such as malaria, typhoid fever and meningitis. Confirmation that symptoms are caused by EBOV infection are made using diagnostic laboratory methods:

- antibody-capture enzyme-linked immunosorbent assay (ELISA)
- antigen-capture detection tests
- serum neutralization test
- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- electron microscopy
- virus isolation by cell culture

RT-PCR tests were the cornerstone of the laboratory response during the 2014–16 West African outbreak. However, for many years the main methods for detection of filoviruses has been virus isolation in cell culture from patient specimens.

Viral load peaks 3–7 days after the onset of symptoms. When patients with EVD present at a hospital, typically 3–6 days after the onset of the symptoms, the viral load is already high and detectable in the patient's blood by RT-PCR in most cases. In fatal cases, viremia is usually 10–100 folds higher than in survivors. IgG and IgM humoral responses develop in survivors but not in all fatal cases thus, diagnosing of EVD using serology is only possible in a fraction of symptomatic patients and requires seroconversion or a substantial increase in antibody titre in paired serum samples. However, serology is the method of choice to diagnose asymptomatic Ebola virus infections, which are characterised by extremely low viremia and development of IgG and IgM about 3 weeks after infection. Another technique also used for post-mortem diagnosis is antigen detection by immunohistochemistry on a skin biopsy.

During the acute phase of the disease and convalescence, viral RNA can be detected by RT-PCR in other body fluids, such as saliva, tears, sweat, breast milk, urine, CSF, ocular fluid, amniotic fluid, vaginal fluid, and seminal fluid. Viral RNA can remain detectable in these fluids after the RT-PCR on blood becomes negative.

2.1.5. Management

Therapeutics

No specific treatment for EVD is currently available. Most investigational therapies for Ebola virus disease aim at the reduction of viral replication to limit the inflammatory storm triggered by viral expansion. Some of these investigational treatments were tested during the 2014–16 Ebola outbreak in West Africa, but clinical trials failed to confirm efficacy of any treatment. Nevertheless, promising experimental interventions were identified. Therapeutics under investigation include ZMapp (Mapp Biopharmaceuticals), a drug comprised of 3 chimeric monoclonal antibodies (mAbs) manufactured in *Nicotiana benthamiana*, the nucleoside analogue inhibitors remdesivir (GS-5734; Gilead Sciences) and BCX4430 (BioCryst Pharmaceuticals), the selective RNA-dependent RNA polymerase inhibitor favipiravir (MediVector), the mAb cocktail REGN3470-3471-3479 (REGNEB3; Regeneron Biopharma), and single-therapy mAb, VRC-EBOMAB092-00-AB (mAb114; Vaccine Research Centre, NIH). Recently interim analysis information was released regarding the PALM trial in DRC, which is a randomized controlled trial of four investigational agents (ZMapp, remdesivir, mAb114 and REGN-EB3), based on which RGN-EB3 and mAb114 seem more promising.

In addition, effective drugs that pass the blood–brain barrier are needed for the management of clinical recurrence of Ebola virus disease and to penetrate immunologically and anatomically preserved sites and reservoirs in survivors beyond the acute phase of the disease.

Currently, management of EVD patients consists on supportive and critical care. Supportive care, i.e. rehydration with oral or intravenous fluids and treatment of specific symptoms, improves survival. In

addition, symptomatic treatment for concurrent infections is provided, tailored to the needs of individual patients.

Prophylaxis

No vaccine against EVD is currently authorised in Europe. Two Ebola vaccines (based on adenovirus constructs) were recently approved in Russia and China, but data seem limited.

In addition to this application for Ervebo, the adenovirus 26 vector EBOV glycoprotein / MVA-BN (Ad26.ZEBOV/ MVA-BN) vaccine regimen developed by Janssen represents another candidate vaccine that has recently been recommended by WHO SAGE after assessment of available data for use in the ongoing DRC outbreak in lower risk populations and with informed consent.

There is an urgent unmet medical need for efficacious and safe preventive vaccines.

About the product

Ervebo (or V920 vaccine as this report will refer to) is a recombinant vesicular stomatitis virus (rVSV) whose gene encoding for the VSV glycoprotein G has been replaced by the gene encoding for the Zaire Ebola virus (Kikwit strain) glycoprotein (rVSVΔG-ZEBOV-GP). The vaccine is a genetically engineered, replication-competent, attenuated live vaccine that induces immune responses after a single dose. The relative contributions of innate, humoral and cell-mediated immune responses to protection from Zaire Ebola virus are unknown.

The pharmacotherapeutic group is viral vaccines (ATC Code J07BX02).

The vaccine is manufactured in serum-free Vero cell cultures. The virus is harvested from the cell culture medium, purified, and frozen to produce the Bulk Drug Substance (BDS). The vaccine Drug Product is a solution for injection manufactured by aseptic addition of the BDS to the Drug Product Stabilizer Solution, which contains 2.5 mg/mL rice derived recombinant human serum albumin (rHSA) and 10 mM Tris buffer. This vaccine contains a trace amount of rice protein. The vaccine must be transported and stored frozen at -80°C to -60°C.

The proposed indication for V920 is for active immunization of at-risk individuals 18 years of age and older to protect against Ebola virus disease caused by Zaire Ebola virus.

The proposed posology is 1 mL of ≥ 72 million plaque forming units (pfu) administered as a solution for injection through intramuscular administration.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on i) the severity and mortality of the disease to be prevented, ii) the unmet medical need due to lack of authorised vaccines or therapeutics for EVD, iii) the V920 efficacy and safety data, which indicated that the vaccine was immunogenic, protective and generally well tolerated. Although certain challenges with maintenance of an accelerated assessment were identified in the pre-submission stage (e.g. generation of certain pharmaceutical data, a new manufacturing site requiring conduct of an inspection during the assessment, and the suitability of batch control testing sites), these limitations were accepted in the context of the urgent high unmet medical need and promising clinical data.

During the assessment, the possibility of a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004 was considered, taking into account the nature of the target condition, emergency situation and applicant's position on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The applicant provided an exhaustive plan to generate the final process validation and comparability data for V920 Drug Substance and Drug Product, which would enable through the fulfilment of the SOs to submit an application to convert the CMA into a full registration by October 2020. The applicant's ability to provide a comprehensive quality dossier is also supported by the two GMP inspections carried out at Burgwedel Biotech GmbH (Burgwedel) in March 2019 and July 2019 by the local health authority GAA, which led to the issuance of GMP certificates and MIA for the site in question. The Applicant considers that the final process validation and comparability reports will confirm the positive benefit-risk assessment of V920 and define a comprehensive quality dossier for the medicinal product. The Specific Obligations proposed by the applicant in Annex II of the SmPC (Section E) define stringent regulatory oversight to ensure submission of emerging CMC information in a specific timeframe. Moreover, the applicant will continue to maintain the EMA and all other stakeholders updated about any acceleration of the manufacturing schedule in consideration of the ongoing EVD emergency.
- Unmet medical needs will be addressed, as V920 has shown to have high protective efficacy and effectiveness in the prevention of EVD, and the data submitted in the framework of the MAA procedure demonstrate that the vaccine has the potential to fulfil unmet medical needs both in endemic and non-endemic regions. In addition V920 was generally well tolerated and had a favourable safety profile.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Ebola virus is a serious pathogen responsible for an unprecedented epidemic in West Africa in 2014-2016, which led to a case fatality rate of approximately 40%. Recently, the WHO declared a PHEIC in the Democratic Republic of Congo (DRC – North Kivu) due to the ongoing outbreak of EVD in that region. The CMA would ensure expedited EU approval, and this will translate into an accelerated WHO prequalification step and consequent early collaborative registration by AVAREF countries. It would also ensure earlier availability of licensed supplies to African countries on the grounds that an expedited approval of the artwork will allow faster ramp-up of manufacturing activities and supply of licensed doses. Use of a licensed product will remove the requirements for GCP training and informed consent, which will accelerate the public health response. Furthermore, use of a licensed product will support vaccination of European health care workers who are being deployed to support the African outbreak currently ongoing under emergency frameworks in some European countries. The applicant is ensuring that V920 is consistently produced and controlled according to quality standards and is minimizing the risks involved in pharmaceutical production that cannot be eliminated through testing the final product. The adoption of the CMA, together with the current accelerated review timetable, will translate into a significant benefit from a public health perspective, which is supported by the overall evidence generated.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a one ml solution for injection containing ≥ 72 million pfu of live attenuated recombinant vesicular stomatitis virus (rVSV) strain Indiana with a deletion of the VSV

envelope glycoprotein (G) replaced with the Zaire Ebola Virus (ZEBOV) Kikwit 1995 strain surface glycoprotein (GP) as active substance.

Other ingredients are: recombinant human serum albumin, trometamol (Tris) buffer and water for injection. Hydrochloric acid and sodium hydroxide are used for pH-adjustment.

The product is available in a single-dose vial (type I glass) with a stopper (chlorobutyl) and a flip-off plastic cap with aluminium seal. The product is available in a pack size of 10 vials.

2.2.2. Active Substance

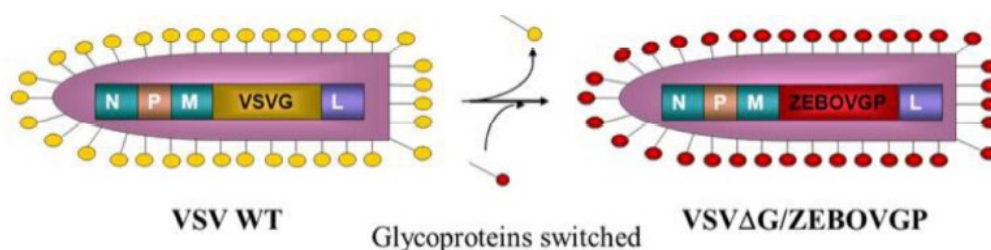
General information

The active substance (AS) (also referred to as the bulk active substance-BAS), (rVSVΔG-ZEBOV-GP, live attenuated) is a live, recombinant viral vaccine.

The Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live attenuated) is a recombinant virus consisting of a single recombinant VSV isolate (11481 nt, strain Indiana) with the gene for the Zaire Ebolavirus GP (ZEBOV-GP), Kikwit strain replacing the gene for the VSV-GP, which has been deleted. This results in a VSV backbone with the ZEBOV-GP constituting the envelope of the virus. As for similar chimeric vaccines, substitution of the native virus GP with a heterologous GP leads to significant attenuation of the virus.

The active substance of Ervebo has never been registered in the European Union and is qualified as a new active substance.

Figure 1. Structure of wild-type VSV and rVSVΔG-ZEBOV-GP Vaccine



Manufacture, characterisation and process controls

The sites responsible for manufacturing, testing and storage of the master/working cell banks and master virus seed and BAS are provided. The manufacturing site for AS commercial production (MSD Site-Burgwedel Biotech GmbH, Im Langen Felde 5, 30938 Burgwedel, Germany) has a valid Manufacturing and Importation Authorisation (MIA) and GMP certificate.

Description of manufacturing process and process controls

The manufacture of the BAS consists of two main parts, the upstream process, which produces the virus, and the downstream process, which purifies the virus. The BAS manufacturing process starts with thawing of a vial of the Vero Working Cell bank (WCB). Vero cells are expanded (first steps in flasks, then in roller bottles) via several passaging steps. When a sufficiently high number of cells have been achieved, cells are infected with the Master Virus Seed (MVS). After incubation, the supernatant fluid (containing the recombinant virus) is harvested. The harvest is clarified using depth filtration. Subsequently, the clarified harvest is treated with benzonase (enzyme to digest residual Vero cell DNA). The resulting intermediate is called the reacted viral harvest, which is further purified and concentrated via ultrafiltration/diafiltration. The ultrafiltered product (UFP) is then formulated into BAS by addition of Tris (trometamol) buffer and recombinant human serum albumin (rHSA). After mixing, the BAS is filled in

specified bags, frozen and stored between -80°C and -60°C. No reprocessing is performed. In-process controls are adequately set to control the process. Details of the container-closure system are provided.

Control of materials

All raw materials, culture media and reagent solutions used in the BAS manufacturing process are described. All raw materials are tested to standards appropriate for their intended use. The qualitative composition of the media used during manufacturing is provided. Irradiated bovine serum (BSE/TSE-free) was used for development and cryopreservation of the MCB.

No materials of primary human or animal origin are used in the manufacture of BAS. Two raw materials, VP-SFM 1X and benzonase, utilise animal-derived components in their manufacturing processes. Based on the manufacturing processes and the testing, the risk for viral contamination is considered to be negligible.

VP-SFM 1X medium contains recombinant human insulin which is derived through yeast (*Pichia pastoris*) fermentation. During purification of insulin, porcine pancreas trypsin is used. The porcine trypsin is obtained from USDA licensed facilities sourced from healthy animals of USA origin. Porcine trypsin undergoes a low pH hold step employed for viral inactivation purposes and does not incorporate the use of bovine lactose.

Benzonase is an enzyme derived from *E. coli* fermentation. The medium used for *E. coli* fermentation contains casamino acids derived from bovine milk sourced from healthy animals in Australia and New Zealand. Casamino acids are isolated using low pH conditions at elevated temperature for an extended period of time followed by oven drying at high heat for an additional extended time. Furthermore, the medium containing the casamino acids is sterilised-in-place using elevated temperature and pressure.

Quality of the raw materials was adequately described (compliant with Ph.Eur. or controlled by in-house specifications).

The master cell bank (MCB) was manufactured by IDT Biologika GmbH using the WHO reference cell bank as starting material. Cells are stored frozen and kept in cryopreservation medium containing 30% irradiated fetal bovine serum and 10% DMSO. The MCB was extensively tested for qualification.

The working cell bank (WCB) was manufactured by Merck, West Point, USA using the IDT MCB as starting material. Cells are stored frozen in serum-free medium containing 20% DMSO in the vapour phase of liquid nitrogen. The WCB was extensively tested for qualification. Some further testing to complete qualification is required (see list of specific obligations). The testing plan for the WCB included in the CTD is deemed sufficient.

The cloning of the rVSV ZEBOV-GP virus consists of reverse genetics placing the ZEBOV envelope glycoprotein gene into the genome of the Indiana strain of vesicular stomatitis virus (VSV) as a substitution for the fusogenic VSV-G envelope glycoprotein. One clone was selected to become the pre-master virus and was tested and then amplified with cells from the Vero MCB to create the pre-master virus seed. Vero cells sourced from the master cell bank were expanded (in serum-free medium) and used to manufacture the master virus seed (MVS) which is stored frozen at -80 to -60 °C. The MSV was extensively tested for qualification. Genetic stability was demonstrated from master virus seed to one viral passage beyond GMP manufacturing level. A WVS has been established. This WVS will be qualified and implemented via a variation procedure post approval in order to have a two-tiered virus seed system but in the meantime, it is acceptable to initiate the manufacturing process directly from the MSV.

Control of critical steps and intermediates

Critical process parameters (CPPs) are defined as process parameters that must be controlled and/or monitored within an established range to ensure quality attributes are met. A critical quality attribute

(CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CPPs for BAS manufacturing arise in unit operations describing cell passage, virus harvest, ultrafiltration and formulation.

CQAs are tested as a part of BAS release. Control cells and harvested control fluid, harvested viral fluid, and bulk BAS are also sampled and tested. Overall, acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

AS process validation-PV (or process performance qualification- PPQ) results are only partially available. Process validation for AS is still ongoing. Data from 1 representative AS lot and 1 engineering batch (which may be considered as representative) were provided. For these lots, the process operated within acceptable limits and the QC test results were within the acceptance criteria and compliant with the specifications. The Burgwedel commercial process is identical to the West Point clinical lot process (also produced at the same scale). As such, if controlled according to the described control strategy, the process is expected to yield AS of the same quality as at the West Point site. West point material produced thus far has been shown to be of adequate and consistent quality. Taken together, these data are considered to be sufficient to support granting of a conditional Marketing Authorisation (CMA) at this point in time. Additional AS PPQ data are requested to be provided post-approval to complete the process validation dataset for the active substance as a specific obligation to the marketing authorisation (See discussion section for more detail).

Results from container-closure integrity and extractable/ leachable studies have been provided and are considered to be adequate.

Manufacturing process development

The bulk active substance (BAS) manufacturing process was developed in three stages.

The BAS manufacturing process was initially developed at IDT Biologika, Germany. At IDT Biologika, a total of thirteen BAS lots and ten finished product lots (FP) were manufactured. Five of the FP lots were utilised in clinical trials, including the ring vaccination trial conducted in Guinea during the 2014-2016 outbreaks.

The BAS process was slightly modified, upscaled and transferred to Merck West Point (PA, US). Additional clinical batches were manufactured at Merck West Point. The BAS manufacturing campaign included four lots, which were manufactured with a modified process from IDT Biologika. Analysis of BAS lots manufactured by IDT Biologika and Merck West Point indicated that both processes generated comparable BAS. The manufacturing process developed at IDT Biologika involved cell culture utilising a Vero MCB and infection using a MVS, both manufactured by IDT Biologika. However, Merck West Point-EUAL lots utilised a Working Cell Bank (WCB) that was manufactured at Merck West Point which was derived from the IDT Biologika MCB. Merck emergency use assessment and listing (EUAL) lots utilised the MVS manufactured by IDT Biologika.

The active substance for the commercial product will be manufactured at the Burgwedel site (Germany). Only minor modifications were introduced in the Burgwedel process (same scale as Merck West Point process).

Although FP lots that comply with the specifications (formulated using within-specification AS lots) are expected to behave similarly in terms of potency as the clinical batches, comparability between clinical material and commercial BAS/FP from Burgwedel needs to be formally demonstrated. These data are requested to be provided post-approval as a specific obligation to the Marketing Authorisation.

IDT Biologika developed a potency assay (plaque assay), which was used to release clinical materials. A different version of the plaque assay has since been validated at Eurofins Lancaster Laboratories, Inc. (ELLI, Lancaster, PA) and will be used for commercial release testing and all future stability studies. The ELLI potency method was developed by MSD based on the initial plaque assay used at IDT Biologika with several changes. Both methods have been validated. Although both methods generate reportable results using PFU/mL as the unit of measure, the two methods are independent of each other and differ in a variety of parameters such as test vessel, cell incubation time and incubation time post inoculation. Furthermore, there is no reference standard to which results are adjusted, thus differences due to multiple factors may result in different reportable potencies. According to the company, the urgent timing associated with the development of this product to support the manufacture of emergency use material did not allow for a complete bridging study powered to support commercial manufacture. The estimated difference between the two methods was calculated and indicating that the ELLI results are overall slightly higher than the IDT Biologika results. This estimated difference was calculated based on data obtained for 3 AS batches. In order to generate potency specifications that are linked to clinical efficacy and safety, clinical batches released using the IDT potency assay were retested using the validated ELLI potency assay. Since long term stability studies to date have shown no loss in potency, the geometric mean of all of the time points has been calculated for the IDT assay results. The values obtained through the retest at ELLI in comparison with the long-term stability data from IDT Biologika are consistent with the difference calculated between the methods. The difference between the two methods was slightly larger than initially observed when comparing 3 AS lots. However, this difference can be considered a consequence of the assay variability and is therefore not unexpected. Overall, therefore use of the validated ELLI potency method for commercial testing is justified.

The applicant has provided the individual batch data (including results for CQAs, total protein, host cell protein, host cell DNA, Tryple activity (residual medium), residual benzonase and aggregate analysis, when available) of all AS batches produced by IDT Biologika and by Merck West Point. It was indicated which batches have been used in the clinical trials (that were found to meet the clinical parameters for safety and efficacy), as well as which batches have been used in the Democratic Republic of Congo. It was also clearly indicated which potency assay was used for each of these batches. Batches met specifications in force at the time.

Characterisation

Two distinct genetic stability assessments have been performed. Virus produced at 3 consecutive viral passage levels was sequenced. No consensus nucleotide changes were observed. The applicant provided a detailed description of the genetic stability analysis of the recombinant virus.

The amount of free Ebola glycoprotein was evaluated as a possible CQA. It is suggested that free Ebola GP (shed GP, sGP) could result in some of the pathogenic effects of Ebola infection. When examining the vaccine sequence, it was determined that the coding region is predicted to preferentially translate the full GP and not the sGP construct. Furthermore, the downstream purification will significantly reduce any free/soluble protein such as the free-GP in the final BAS. Since other markers of protein clearance have been evaluated during analytical comparability between the IDT Biologika manufacturing process and MSD Site-Burgwedel Biotech GmbH manufacturing process, it was concluded that the free Ebola-GP itself is not considered a CQA.

Particle distribution and aggregation have been assessed. Flow cytometry-based analysis shows no observable aggregation. The results also show no apparent change in the viral particle size or distribution after storage at 37°C for 24 hours, while the plaque assay shows a significant decrease in the infectivity of this material.

A comparison of the genome quantification data and genome particles/plaque forming units (pfu) ratios was performed. The genome copy:PFU ratio appears consistent across different lots manufactured at different facilities and different scales.

Potency was assessed on various BAS lots at different stages during production (harvest, clarified harvest, reacted harvest, bulk active substance). Potency was shown to be consistent between different lots for all stages.

Harvested virus fluid samples from the PPQ campaign were subjected to next generation sequencing to provide evidence of virus identity and genetic stability.

Measurement of process residuals and host cell impurities (HCP) during process development has demonstrated sufficient removal of impurities during the BAS process. The consistency of benzonase and host cell protein (HCP) clearance through the ultrafiltration process was shown. HCP clearance was determined to be >93%, thus reducing HCP to clearly acceptable levels in the ng/mL range. Furthermore, benzonase clearance (>99%) may be an appropriate surrogate for HCP clearance, given the consistent patterns observed for the two markers. The following residuals and host cell impurities are assumed to be cleared similarly to benzonase (~30 kDa), a surrogate for similar and smaller molecular weight impurities: TrypLE, EDTA and trypsin inhibitor. Stated impurities have been present in product used in clinical trials.

Characterisation has been performed for AS material from IDT Biologika and/or Merck West Point. The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure.

Specification

The AS release specifications are presented. Release tests include testing on control cells and the harvested control fluids (cell culture), on the harvest and on the bulk active substance.

Host cell DNA and residual benzonase content are considered important quality attributes of the active substance that should at least be determined until enough evidence has been generated to conclude on the robust and reliable reduction of these impurities below an acceptable limit. The applicant has included testing for host cell DNA and residual benzonase as an in-process control (IPC) with acceptance criteria. Upon demonstration of consistency on a sufficiently high number of batches, these routine tests may be removed.

As regards host cell protein, the applicant will monitor HCP via total protein analysis at the level of the ultrafiltration product. Upon qualification, this method will be implemented post-approval as an IPC in the relevant sections of the CTD (see list of specific obligations). The applicant will retroactively test previously manufactured AS PPQ lots (AS PPQ lots 1, 2, 4, and 5). The applicant will also mention IPC results of impurity testing on the release certificates and on the information provided to the Official Medicines Control Laboratory (OMCL). Given that benzonase clearance may be indicative for HCP clearance, the applicant's approach to temporarily release AS lots without result for total protein at UF product is acceptable, provided the residual benzonase levels are within the acceptance limits.

Analytical methods

Descriptions were provided for the analytical methods used for AS release testing. All methods were properly validated or qualified (see separate discussion on identity assay below). The following methods were performed as described by Ph.Eur.: haemadsorption, sterility, mycoplasma (PCR, indicator cell line and broth and agar), mycobacteria, pH and appearance. Non-compendial methods included cell line identity by cytochrome oxidase testing, adventitious agents *in vitro*, adventitious agents *in vivo*, reverse transcriptase activity, identity and potency.

Potency assay: The potency of the BAS is obtained using a plaque assay. The plaque assay is a test in which a dilute solution of virus is applied to a tissue culture dish containing a layer of host cells. After incubation, cells are stained for visualisation and the plaques are counted. The number of infective virus particles in the original solution is estimated based on the number of plaques.

Identity assay: For the identity assay, a plaque assay (similar to the potency assay) is performed which is followed by an immunostaining. 100% of the plaques must be positive by immunostaining to confirm the identity of the sample as Ebola Zaire BAS. Because of the criticality of the polyclonal antibody (used for identity release test), additional data is required to complete the qualification. As part of the qualification of the polyclonal antibody therefore, to demonstrate the specificity of the polyclonal antibody, the company should also include a negative control with Vero cells infected with wild type vesicular stomatitis virus: these should also yield a negative result (see list of specific obligations).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch data of the AS PPQ batches were not yet available at the time of MAA submission. These have been requested to be provided post-approval as a specific obligations to the Marketing Authorisation. However, an appropriate number of BAS lots have been produced (at IDT Biologika, Germany, and Merck West Point (PA, US)) of which some have been used to manufacture several FP used in clinical studies. The active substance for the commercial product will be manufactured at the Burgwedel site (Germany). Only minor modifications were introduced in the Burgwedel process (same scale as Merck West Point process) and the specifications are similar. Therefore, the submission of AS PPQ batch data post-approval is justified.

Reference materials

No reference standards are used in testing of the BAS. However appropriate positive controls (which need to be within established acceptance criteria) are used to verify validity of the potency assay in order to confirm the correctness of the potency results.

Container closure system

BAS is stored frozen at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ in single-use specified bags. The bags comply with compendial criteria. Suitability and compatibility of the bags was demonstrated. Extractables testing has been performed; the outcome of a study to define the need for them indicated that no leachables testing was required.

Stability

The applicant proposes a specified AS shelf life when stored at $-70 \pm 10^{\circ}\text{C}$.

An expiry extension is planned to be filed when real time stability data from three or more historical lots become available.

The applicant has provided some stability data for the IDT Biologika lots and Merck West Point lots.

Real time stability data (below -60°C) are available for specified IDT Biologika lots and for Merck West Point lots. All results comply with the specifications. No decrease or trend is observed for potency (also not at specified accelerated conditions). These batches are considered to be representative enough for the commercial site and can therefore be considered to support the claimed shelf life until additional data are available. Stability data for AS from the commercial Burgwedel site will be provided post-approval.

Current data support the proposed shelf life. However, the applicant is requested to complete the package of supporting stability data by fully demonstrating the comparability of Burgwedel PPQ batches with the clinical batches as a specific obligation to the Marketing Authorisation.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The vaccine finished product is a solution for injection manufactured by aseptic addition of the BAS to the finished product stabiliser solution, which consists of recombinant human serum albumin (rHSA), Trometamol, and Water for Injection. The vaccine is filled at a volume of 1 ml into single-dose vials. The glass vial is stoppered and capped with flip-off plastic caps and aluminium overseals. The FP appears as a colourless to slightly brownish yellow liquid with no particulates visible. The composition of the final FP is provided in table 1 below. There are no overages. The current FP formulation has the same composition and pharmaceutical form as that used in historical clinical trials where safety and efficacy was established.

Table 1. Composition of the Finished Product

Active Ingredients	Concentration	Amount per 1 mL	Function
Live attenuated rVSV expressing the glycoprotein of Zaire Ebola Virus in place of the VSV glycoprotein (rVSVΔG-ZEBOV-GP)	$\geq 7.2 \times 10^7$ pfu/mL	$\geq 7.2 \times 10^7$ pfu	Active
Inactive Ingredients	Function		
Trometamol (Tris)	Buffer		
Recombinant Human Serum Albumin (rHSA)	Stabilizer		
Water for Injection	Quantity Solvent		

The excipient used in Ebola Zaire Vaccine is a purchased finished product stabiliser solution consisting of trometamol buffer -Tris (Ph.Eur.), recombinant human serum albumin (rHSA) stabiliser and water for injection (Ph.Eur.). The tests performed on the finished product stabiliser solution are provided.

The recombinant human serum albumin is considered a novel excipient. Detailed information was provided on the structure; general properties, manufacturer, manufacturing process and controls, characterisation, specifications, analytical methods, batch data, container and stability of the rHSA. The lyophilised rHSA is manufactured and released by a third company in compliance with a defined set of specifications (including purity), and this product has a limited shelf life. The stabiliser solution contains rHSA, Tris buffer and WFI (Tris and WFI comply with Ph.Eur.), and has a specified shelf life. The specifications of the stabiliser solution were provided. Information on the manufacture of the stabiliser solution (including process controls) is described in the MAA. The buffer is purchased from a qualified supplier.

The FP has been manufactured at the following facilities: 1) IDT Biologika GmbH, Germany; 2) Merck West Point, Pennsylvania; 3) MSD Site-Burgwedel Biotech GmbH, Germany.

There have been no major changes during the manufacturing process development. For the first batches, different stopper material and already sterilised buffer has been used. There are small differences between the manufacturing processes in West Point and Burgwedel, which are considered to be marginal. In addition, there have been no changes in the product composition or pharmaceutical form during development. A risk assessment approach was used throughout the development of the FP manufacturing process. The purpose of the process risk assessments were as follows: 1) Identify parameters that are most likely to impact product quality and process performance to guide and prioritise the focus of process development and Process Performance Qualification readiness activities; 2) Understand and document the relationship between product and process attributes and process parameters and materials; 3) Identify process failure modes and mitigation plans to support the process control strategy. Development studies were identified and executed based on the initial risk assessment.

As already stated, IDT Biologika developed the potency assay (plaque assay), which was used to release clinical materials and a different version of the plaque assay was validated at Eurofins Lancaster Laboratories, Inc. (ELLI, Lancaster, PA) to be used for commercial release testing and all future stability studies. The ELLI potency method was developed by MSD based on the initial plaque assay used at IDT Biologika with several changes to ensure a robust method. Both methods have been validated. The results obtained by the ELLI method are slightly higher than those obtained by the IDT method (but still within method variability). This is acceptable.

The FP container closure system consists of a 2R Type-1 class B borosilicate clear glass tubing vial (compliant with Ph.Eur), a 13 mm chlorobutyl stopper (compliant with Ph.Eur) and a 13 mm flip-off aluminium seal. Extractables testing of the vials and the stoppers has been performed.

Ervebo is provided in single-dose vials without preservative. The FP is manufactured by aseptic addition of sterile BAS and FP stabiliser solution. The formulated bulk is aseptically filled into vials. Sterility testing is included as part of release testing. Process simulations verify the robustness of the aseptic processing steps. Additional integrity of the filled vials is provided by container closure integrity (CCI) validation.

Manufacture of the product and process controls

Product specification

The FP release and stability specifications are provided and include appropriate specifications for identity, potency, purity and physico-chemical attributes. The proposed specifications are considered to be properly justified. Identity testing (which is considered as complementary to the plaque assay to assess potency) will also be performed on 3 FP lots during stability testing.

The currently proposed batch control testing sites are located in the US. The finished product manufacturing site is currently unable to place a unique identifier on the FP. See discussion below.

Analytical methods

Descriptions were provided for the analytical methods used for FP release testing. All methods were properly validated or qualified. Specified methods were performed as described by Ph.Eur.

The potency assay and the identity assay are the same as the ones used for the active substance. AS and FP have the same matrix (only the virus titre is different).

Batch analysis

The applicant has provided the individual batch data from a number of FP batches produced thus far (from IDT and from West Point), including batches used in the clinical trials (that were found to meet the clinical parameters for safety and efficacy), as well as batches that have been used in the Democratic Republic of Congo. Batch data complied with specifications in force at that time. It was also clearly indicated which potency assay was used for each of these batches. The applicant should provide the FP batch analysis data of the PPQ batches (Burgwedel site) (see list of specific obligations).

Regarding impurities, residual host cell DNA and residual benzonase tests are performed on BAS but the acceptance criteria are applied to the final filled container by calculation. The potential risks related to elemental impurities have been suitably evaluated. No additional impurities are introduced in the formulation and filling process of Ervebo.

Reference materials

No reference standards are used in testing of the FP. However appropriate positive controls (which need to be within established acceptance criteria) are used to verify validity of the potency assay in order to confirm the correctness of the potency results.

Stability of the product

A FP shelf life of is 36 months for finished product stored at $-70\pm 10^{\circ}\text{C}$ is proposed.

An expiry extension to up to 60 months is planned to be filed when real time stability data from three or more historical lots become available.

The applicant has provided stability data for the IDT Biologika lots and Merck West Point lots. Stability data for FP from the commercial Burgwedel site will be provided post-approval. For the stability testing of the 3 FP PPQ lots from Burgwedel, the applicant will also include identity testing. The identity assay does not only serve to confirm correct identity but also to complement the potency assay. The PFU assay (proposed potency assay) only measures the titre of the recombinant virus but does not provide information about the expression of the GP. As such, a combination of the potency assay (PFU assay) and identity assay (GP immunostaining) is considered necessary to properly assess potency during shelf life (stability testing).

Real time stability data (below -60°C) are available up to 48 months for 8 IDT Biologika lots and 3 Merck West Point lots. All results comply with the specifications. No decrease or trend is observed for potency (also not at accelerated conditions, i.e. at -40°C).

Preliminary evaluation indicated that the vaccine product may be sensitive to light exposure. The secondary packaging (market box) is expected to protect vaccine vials from light. Samples from full scale batches will be subjected to a confirmatory photo-stability study and to demonstrate that the secondary packaging (market box) protects the FP from light exposure. The SmPC states that the vial should be kept in the outer carton in order to protect from light.

The SmPC also states 'After thawing, the vaccine should be used immediately; however, in-use stability data have demonstrated that once thawed, the vaccine can be stored for up to 14 days at 2°C to 8°C prior to use. At the end of 14 days, the vaccine should be used or discarded. Upon removal from the freezer, the product should be marked with both the date that it was taken out of the freezer and also a new discard date (in place of the labelled expiry date). Once thawed, the vaccine cannot be re-frozen.'

Confirmatory studies will be performed to support post-thaw product exposure to elevated temperature and exposure times. A total of 2 weeks at $2-8^{\circ}\text{C}$ and 4 hours at up to 25°C are supported by the potency

specification assessment. Stability testing, after samples are exposed to the elevated temperature / times, will be performed to further support the allowance time period.

The stability data support the proposed shelf life of 3 years. A shelf life of 3 years for the commercial FP is therefore acceptable. Comparability must however be comprehensively demonstrated between Burgwedel batches and AS/FP material from IDT and West Point. These data are requested post-authorisation as a specific obligation to the Marketing Authorisation.

Adventitious agents

Cell substrates, virus seeds, and raw materials used during manufacture of Ervebo are rigorously tested, using validated methods, to provide high confidence that extraneous agents are not present in the FP. The seed viruses are derived from Vero cell systems under conditions similar to those used in the vaccine bulk production. Two raw materials, namely VP-SFM 1X (which contains recombinant human insulin which itself uses porcine trypsin in its manufacture and also used for cell bank establishment) and benzonase (produced using bovine milk fit for human consumption), utilise animal-derived components in their respective manufacturing processes. VP-SFM 1X is used during cell bank and active substance manufacture and benzonase only in AS manufacture. The master virus seed and the cell bank system were properly tested. No animal-derived materials are used in the manufacturing processes of AS and FP. Risk of bovine spongiform encephalopathy (BSE) contamination is negligible. Irradiated bovine serum was used for development and cryopreservation of the MCB.

During AS/FP production, various routine testing is performed to guarantee the absence of adventitious agents. BAS is tested for sterility; the virus harvest is tested for sterility, mycoplasma, mycobacteria, retrovirus and adventitious agents (*in vitro* tests); control cells (from virus culture) are tested for sterility, mycoplasma and adventitious agents (*in vitro* and *in vivo* tests). FP is tested for sterility and endotoxin.

GMO

Please refer to the non-clinical ERA evaluation for the GMO evaluation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of deficiencies were highlighted relating to: the Manufacturing and Importation Authorisation (MIA) and GMP certificate for the active substance (AS) and finished product (FP) manufacturing site, process validation for AS and FP and comparability data; impurity testing; completion of viral safety testing of the master cell bank (MCB) and working cell bank (WCB) and additional qualification of a reagent used in the identity assay. These deficiencies were classified as Major Objections (MOs) in order to ensure completion of the data set by the applicant at appropriate time points, e.g. as specific obligations, see below. As a result, the marketing authorisation is conditional on the applicant providing responses to the requested data.

The GMP / MIA for the AS/FP site was subsequently granted and this MO was therefore resolved.

Data have been submitted by the company during the procedure in relation to the other MOs and CHMP has considered that these data would support grant of a conditional Marketing Authorisation (CMA) on quality grounds, taking into account the public health emergency of international concern declared by WHO. However, a number of specific obligations (SOs) are needed in order to complete the manufacturing process details.

A summary of the status of the information, including the specific obligations and their rationale and additional recommendations for further development are discussed below.

Specific Obligations

Stability data were provided for clinical AS and FP lots. The currently available stability data support an AS shelf life of 36 months and a FP shelf life of 36 months. However, these stability data were derived from IDT and West Point batches (clinical batches). In the framework of a conditional marketing authorisation, a shelf life of 36 months can be granted for the commercial product (AS and FP). However, it is expected that comparability is comprehensively demonstrated post-approval between commercial and clinical batches (see list of specific obligations) in order to confirm the shelf life of the commercial product. Furthermore, given the limited experience of the Burgwedel site with the manufacturing process, the applicant is also requested to provide the AS and FP stability data from the Burgwedel AS process performance qualification (PPQ) batches when the stability studies have been finished (post-approval) (see list of recommendations). Any out-of-specification (OOS) results or trends should be communicated to the authorities as soon as possible. In addition, to confirm the stability of the vaccine during a short time exposure to elevated temperatures, also the results of the post-thaw FP stability data from the 36 month time point should be provided (post-approval) when these are available (see list of recommendations).

Process validation (or process performance qualification) for both AS and FP is still ongoing. Data from 1 representative AS lot and 1 representative FP lot were provided. For these lots, the process operated within acceptable limits and the QC test results were within the acceptance criteria and compliant with the specifications and support grant of a conditional Marketing Authorisation. Unexpected issues arose during AS PPQ, delaying the availability of complete AS PPQ data. However, the root cause of the problem has been identified and proper measures have been taken to avoid similar problems in the future. This was discussed during the GMP inspection and the measures were deemed acceptable by the GMP inspectors.

The Burgwedel commercial process is identical to the West Point clinical lot process (also produced at the same scale). As such, with the described control strategy in place, the process is expected to yield AS of the same quality as at the West Point site. West point material produced thus far has been shown to be of adequate and consistent quality. However, CHMP is of the view that two further active substance lots (AS PPQ 4 and 5) are required to complete the information by providing sufficient comprehensive evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce the medicinal product, meeting its predetermined specifications and quality attributes. In the framework of a conditional marketing authorisation therefore, additional process validation data for AS and FP has been requested post-approval to confirm the validated status of the process as a specific obligation to the Marketing Authorisation.

The proposed sites for batch control testing are located in the US and the applicant has submitted a plan to transfer FP release testing to a site in EU by July 2022 (latest date for the last test to be transferred). The identified required steps and timelines in the plan are considered appropriate. In view of the Public Health Emergency of International Concern declared by the WHO and in order to ensure early supply of this medicinal product in the context of this emergency, granting of an exemption for batch control testing in a third country is supported, in line with the submitted plan for transfer of testing. Annual reports on progress on transfer of testing are requested.

The Burgwedel manufacturing site is currently unable to place a unique identifier on the FP. However, the applicant is seeking exemptions from competent authorities of Member States that would be willing to accept this product on their market without the unique identifier, in light of the public health emergency. In the absence of any such exemption, the unique identifier is still required, therefore the manufacturer should implement serialisation at the earliest opportunity to allow placing of the product on the market upon expiry of exemptions.

Although FP lots that comply with the specifications (formulated using within-specification AS lots) are expected to behave similarly in terms of potency as the clinical batches, comparability between clinical

material and the commercial product manufactured at the Burgwedel site must be demonstrated. This is to justify that the commercial product is representative of the clinical product (and thus that the clinical data and conclusions are also applicable for the commercial product). In the framework of a conditional marketing authorisation, comparability between clinical material and the commercial product will need to be demonstrated post-approval as a specific obligation to the marketing authorisation.

In the framework of the conditional marketing authorisation therefore, to complete the manufacturing process details, the applicant should fulfil, post-approval, the following specific obligations (SOs).

SO1: The MAH should provide additional data to confirm that the active substance (AS) process is properly validated. Process and batch data from at least 3 representative AS batches should be provided.

SO2: The MAH should provide additional data to confirm that the finished product (FP) process is properly validated. Process and batch data from at least 3 representative FP batches should be provided.

SO3: The MAH should provide comprehensive comparability data confirming that the commercial product manufactured at the Burgwedel site is representative of the material used in the clinical trials.

SO4: The MAH should complete master cell banks (MCB)/working cell bank (WCB) qualification to include also tests for specified viruses.

SO5: The MAH should provide additional qualification data for the critical reagent used in the identity test (quality control release test for AS and FP).

SO6: The MAH should develop and introduce an active substance in-process control for total protein with appropriate acceptance criteria.

As regards SO1, SO2 and SO3, the following data is requested to be provided in order to complete the information on the adequate validation of the AS process and the FP process and to demonstrate comparability between the commercial product and the clinical material.

a) The process validation data for the PPQ AS batches (Burgwedel site) are requested to be provided. These should not be limited to critical quality attributes (CQA) and critical process parameter (CPP) results but should also include results of all process operating conditions mentioned in the tables in section S.2.2. of the dossier. Given the issues observed during AS PPQ2 and AS PPQ3, two further representative active substance lots (AS PPQ 4 and 5) will be required to provide sufficient comprehensive evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce the medicinal product, meeting its predetermined specifications and quality attributes. Batch data from at least 3 representative and compliant AS batches, in total, should be provided and included in section S.4.4 of the CTD.

b) The applicant is requested to submit process validation data for the PPQ FP batches (Burgwedel site). These should not be limited to CQA and CPP results but should also include results of relevant process parameters (e.g. AS thaw time, mixing time of final formulated bulk- FFB,...). CQAs should also include the FP identity, since the plaque assay (potency) does not provide information about the expression of the GP. As such, a combination of the potency assay (PFU assay) and identity assay (GP immunostaining) is considered necessary to properly assess potency. Also results of hold times, time-out-of-refrigeration (TOR) and total processing time should be provided. It is expected that limits for these parameters will be challenged in the FP process validation studies. Batch data from at least 3 representative and compliant FP batches, in total, should be provided and included in section P.5.4 of the CTD.

c) The applicant is requested to submit comparability analysis data for the Burgwedel site demonstrating that AS/FP from Burgwedel is representative of the AS/FP used in the clinical trials. As regards the comparability analysis, the applicant should provide all relevant process/batch data (intermediates, AS and FP) from batches produced at IDT and at West Point.

d) As part of the AS characterisation and process validation, the applicant is requested to provide results of genome quantitation and aggregate formation (analysed by dynamic light scattering- DLS) of the Burgwedel AS PPQ lots. Particle size testing by DLS should also be performed on 3 AS PPQ lots and 3 FP PPQ lots during stability testing.

e) As part of the FP characterisation and process validation, the applicant is expected to perform an identity test (which is considered as part of the potency test) during stability testing on three Finished Product PPQ batches.

f) As part of the FP process validation, to validate the option of using more than 1 AS lot for FP formulation, at least one of the FP PPQ lots should be formulated from at least 2 AS lots. In addition, one FP PPQ batch should challenge the maximum batch size.

g) Because of the heat sensitivity of the active substance, additional process controls should be implemented to sufficiently control the manufacturing process and in particular possible exposure of the vaccine virus to elevated temperatures. Therefore, when additional process experience has been gained and additional process data are available, the following should be implemented:

(1) The applicant is requested to set a proper and reasonable upper limit for the thawing time of master virus seed (MVS) and working virus seed (WVS), avoiding exposure of the virus to high temperature longer than needed.

(2) To properly control the AS process and to limit the time out of refrigerator of the virus to a minimum, it is strongly recommended to implement an upper limit for the total time of AS exposed to room temperature during downstream purification (from harvest to freezing of AS). Furthermore, since virus degradation is known to occur more rapidly at higher temperatures, the company should introduce a separate process parameter for exposure time to 37°C during the benzonase reaction.

h) The applicant states that the active substance opalescence can span from the specification limit to above the highest standard employed in the compendial method. It appears that this wide range is due to the limited manufacturing experience so far. The applicant is requested to adequately tighten the physical assessment limits with increasing numbers of batches produced and tested. The applicant is reminded that specifications are important measures of batch to batch consistency within a defined and acceptable range and that the current specification does not allow for any relevant control of vaccine appearance.

i) A post-thaw stability study (at 25°C) should be performed (to support post-thaw finished product exposure to elevated temperature exposure times) on the FP as described in section P.8.1.2.2. Since it will take quite some time before the 36 month time point results from this post-thaw stability study will be available, it is deemed sufficient that for the specific obligation of the CMA only the data from the "0" month time point are needed from this post-thaw study. The 36 month results should also be provided (when available), but these data only will not postpone a possible conversion from a CMA to a normal MA. So, whereas the "0" month time point data will be required for the SO, the 36 m data will be requested in the final report as a recommendation.

As regards SO4 (*The MAH should complete master cell banks (MCB)/working cell bank (WCB) qualification to include also tests for specified viruses.*), the applicant is asked to address the following. Whereas the metagenomics analysis is considered a useful tool to screen for other possible viral contaminants,

known/relevant potential viruses should preferentially be screened using more reliable and robust methods that are easier to qualify.

As regards SO5 (*the critical reagent for the identity test (QC release test) should be properly qualified*), because of the criticality of the polyclonal antibody (used for identity release test), additional qualification is required. As part of the initial qualification of the polyclonal antibody, to demonstrate the specificity of the polyclonal antibody, the company is expected to include a negative control with Vero cells infected with wild type vesicular stomatitis virus: these should also yield a negative result (no immunostaining observed).

As regards SO6, it is noted that routine testing for host cell protein in AS has not been included yet in the CTD. The applicant has proposed to monitor HCP via total protein analysis at the level of the ultrafiltration product. Upon qualification, this method will be implemented post-approval as an IPC in the relevant sections of the CTD. The applicant is asked to provide data from tests of previously manufactured AS PPQ lots (AS PPQ lots 1, 2, 4, and 5). Given that benzonase clearance may be indicative for HCP clearance, the applicant's approach to temporarily release AS lots without result for total protein at UF product is acceptable, provided the residual benzonase levels are within the acceptance limits. However, given the limited experience with the Burgwedel process, proper control of HCP (via total protein analysis) is deemed essential and should be implemented as soon as possible as an IPC with acceptance criteria in the relevant sections of module 3 of the CTD. It is also expected that the results of the impurity testing will be mentioned on the release certificates and on the information sent to the OMCL.

Rationale for the specific obligations:

SO1 and SO2: The Burgwedel commercial process is identical to the West Point clinical lot process (also produced at the same scale). As such, if properly controlled, the process is expected to yield AS of the same quality as at the West Point site. West point material produced thus far has been shown to be of adequate and consistent quality. Burgwedel manufacturing is therefore conditionally accepted on the basis that the technology has been transferred and a GMP certificate has been granted. However, the available process validation data for AS and FP do not allow a final conclusion on the validated status of the manufacturing process to be made. The MAH is requested to provide additional PPQ data to confirm that the AS and FP processes are properly validated. Process and batch data from 3 representative batches of both AS and FP are requested.

SO3: Currently, comparability between clinical material and the commercial product manufactured at the Burgwedel site has not been comprehensively demonstrated. Although FP lots that comply with the specifications (formulated using within-specification AS lots) are expected to behave similarly in terms of potency as the clinical batches, demonstration of comparability is required to justify that the commercial product is representative of the clinical product (and thus that the clinical data and conclusions are also applicable for the commercial product). The AS shelf life and FP shelf life (36 months) are based on stability data derived from IDT and West Point batches (clinical batches). Comparability between clinical material and the commercial product must be comprehensively demonstrated.

SO4: Although the applicant has provided reassurance on the viral safety of the cell bank system using a combination of specific tests and metagenomics analysis, additional testing should be performed on the MCB (or WCB) using a robust, reliable and qualified method (e.g. classic PCR). It is currently very difficult (if not impossible) to qualify metagenomics approaches with regard to sensitivity, specificity and limit of detection. Therefore, given the potential viral contaminants of Vero cells, properly qualified methods are requested and should be implemented to confirm the absence of these viruses from the MCB or WCB (which is in line with current standards and GMP for qualification of cell bank systems).

SO5: Since the potency assay only quantifies the amount of infectious virus without making distinction between the recombinant vesicular stomatitis virus (VSV) and any possible wild type VSV, the identity

assay is the only assay which confirms the correct identity of the recombinant vaccine virus. As such, proper qualification of the critical reagents used in this assay is of importance. Initial qualification of the polyclonal antibody used in the identity test included as negative controls only uninfected Vero cells, damaged Vero cells, and MRC-5 cells infected with varicella zoster virus. However, to demonstrate the specificity of the polyclonal antibody, the company is asked to include as part of the initial qualification of the polyclonal antibody also a negative control with Vero cells infected with wild type vesicular stomatitis virus: these should also yield a negative result (no immunostaining observed). Without this qualification, it cannot be concluded that the release testing panel for AS/FP is capable of discriminating between the recombinant vaccine virus and possible wild type VSV.

As regards SO6, it is noted that routine testing for host cell protein in AS has not been included yet in the CTD. The applicant has proposed to monitor HCP via total protein analysis at the level of the ultrafiltration product. Upon qualification, this method will be implemented post-approval as an IPC in the relevant sections of the CTD. The applicant has committed to retroactively test previously manufactured AS PPQ lots (AS PPQ lots 1, 2, 4, and 5). Given that benzonase clearance may be indicative for HCP clearance, the applicant's approach to temporarily release AS lots without result for total protein at UF product is acceptable, provided the residual benzonase levels are within the acceptance limits. However, given the limited experience with the Burgwedel process, proper control of HCP (via total protein analysis) is deemed essential and should be implemented as soon as possible as an IPC with acceptance criteria in the relevant sections of module 3 of the CTD. It is also expected that the results of the impurity testing will be mentioned on the release certificates and on the information sent to the OMCL.

In conclusion, the quality part of the current dossier may be approved as a conditional MA with a list of specific obligations that need to be fulfilled to complete the manufacturing process details. In addition, the applicant is also requested to take into account the list of recommendations.

Recommendations

The applicant has provided detailed descriptions of the manufacturing process, the control of materials, the process controls (including critical process parameters (CPPs)) and the process development, for both the AS and the FP. The cell bank system and virus seed system were adequately qualified. To ensure sufficient vaccine supply in the future from the current virus seed system (which only contains a master virus seed), the applicant is recommended to establish a 2-tiered virus seed system by implementing also a working virus seed (WVS). Use of the WVS can be submitted post approval via a variation procedure (see section- Recommendation(s) for future quality development).

AS and FP specifications were provided as well as detailed information on the analytical methods, which were properly validated or qualified. Container closure systems for AS and FP were described. To confirm the quality and suitability of the finished product containers, the applicant is requested to determine the identity of the two unknown leachables as observed in the leachables studies, and report results when available (see section- Recommendation(s) for future quality development).

Routine testing of residual benzonase and host cell DNA impurities has been included as an in-process control (IPC) with acceptance criteria. As regards host cell protein (HCP), the applicant will monitor HCP via total protein analysis at the level of the ultrafiltration (UF) product. Upon qualification, this method will be implemented post-approval as an IPC in the relevant sections of the CTD (see list of specific obligations). The applicant will retroactively test previously manufactured AS PPQ lots (AS PPQ lots 1, 2, 4, and 5). The applicant will also mention IPC results of impurity testing on the release certificates and on the information provided to the Official Medicines Control Laboratory (OMCL). Given that benzonase clearance may be indicative for HCP clearance, the applicant's approach to temporarily release AS lots without result for total protein at UF product is acceptable, provided the residual benzonase levels are within the acceptance limits.

Host cell protein has been evaluated in clinical IDT lots. As the Burgwedel site has currently limited experience with the manufacturing process, UF total protein results of batches tested retroactively should be provided when available in order to demonstrate consistency and confirm adequate quality of these batches (see list of recommendations). In addition, the currently proposed acceptance limits for residual benzonase and host cell DNA IPC are acceptable for the time being, but when sufficient batch data are available, the applicant should re-evaluate the acceptance limits for impurities (DNA, benzonase and HCP). Based on the results, revision/tightening of these limits should be considered and proposed in a post-authorisation procedure (see section- Recommendation(s) for future quality development).

Both the AS and the novel excipient recombinant human serum albumin (rHSA) have been characterised in detail. Whereas additional testing that was used for characterisation is not required for routine testing, it is important that these methods remain available as characterisation tests to be used in the future in case of relevant changes/variations (for comparability analyses). In particular, for AS, the tests for residual impurities (benzonase, HCP, Tryple activity, etc.) should be maintained, whereas for the rHSA excipient the tests for aggregates (SEC-HPLC), water content and host-cell protein (HCP) should be kept as characterisation tests (see section- Recommendation(s) for future quality development).

Although suitable information about the rHSA excipient has been provided, which is considered an important component of the final finished product, the applicant is requested to provide supplemental validation data for accuracy, linearity and range for both the Tris and rHSA assays (for QC testing of excipient) (see section- Recommendation(s) for future quality development).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

During the procedure, several MOs were raised relating to: the MIA and GMP certificate for the active substance -AS and finished product -FP manufacturing site, process validation for AS and FP and comparability data; impurity testing; completion of viral safety testing of the MCB and WCB and additional qualification of a reagent used in the identity assay. The GMP / MIA for the AS/FP site was subsequently granted and this MO was therefore resolved. Data have been submitted by the company during the procedure in relation to the other MOs and CHMP has considered that these data would support granting of a conditional Marketing Authorisation on quality grounds taking into account the public health emergency of international concern declared by WHO. In conclusion, the quality part of the current dossier may be approved as a conditional MA with a list of specific obligations that need to be fulfilled, as detailed in the assessment report (see discussion section). In addition, the applicant is also requested to take into account the list of recommendations for future development.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. As soon as the total protein assay (to monitor host cell proteins- HCP) is qualified, active substance (AS) lots that have been released without quality control results for total protein at ultrafiltration (UF) product should be tested retroactively and results should be communicated to the Agency and the Rapporteurs.
2. When sufficient batch data are available, the applicant should re-evaluate the acceptance limits for impurities (DNA, benzonase and HCP). Based on the results, revision/tightening of these limits should be considered.
3. With regard to the finished product (FP) leachables studies, the applicant is requested to determine the identity of the two unknown leachables and report results when available.

4. The applicant is requested to provide supplemental validation data for accuracy, linearity and range for both the Tris and recombinant human serum albumin (rHSA) assays (control of excipient).
5. The applicant is requested to provide the remaining AS stability data from the Burgwedel AS process performance qualification (PPQ) batches when the stability studies have been finished (post-approval). Any out-of-specification OOS results or trends should be communicated to the authorities as soon as possible.
6. The applicant is requested to provide the remaining FP stability data from the Burgwedel FP PPQ batches when the stability studies have been finished (post-approval). Any OOS results or trends should be communicated to the authorities as soon as possible.
7. The applicant is requested to provide the post-thaw FP stability data from the 36 month time point when these are available.
8. The applicant is recommended to establish a 2-tiered virus seed system by implementing also a working virus seed- WVS. Use of the WVS can be submitted post approval via a variation procedure.
9. The applicant should keep the tests for residual impurities (benzonase, HCP, host cell DNA and Tryple activity) as characterisation tests for relevant future variations (for comparability analyses: to demonstrate that impurity levels are still within acceptable limits).
10. The tests for aggregates (SEC-HPLC), water content and host-cell protein (HCP) should be kept as characterisation tests for rHSA to be used in case of relevant future changes in the rHSA manufacturing process.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical evaluation comprises a series of pharmacological studies and a toxicological testing program which covers local tolerance and general toxicity in repeat-dose toxicity studies, and a developmental and reproductive toxicity (DART) study. Other studies were also conducted, such as *in vivo* biodistribution and persistence study and an exploratory neurovirulence study.

Pivotal toxicology studies including repeat-dose toxicity studies in mice and cynomolgus macaques, the DART study in rats, and the biodistribution study in cynomolgus macaques are claimed to be GLP-compliant. Primary pharmacodynamics studies, an exploratory neurovirulence test and an exploratory immunogenicity and viremia study were non-GLP.

2.3.2. Pharmacology

The primary pharmacodynamic properties of V920 were evaluated in multiple non-GLP immunogenicity and prophylactic efficacy studies in rodents and in non-human primates (NHP) as summarized in the list below:

- Published evaluations of prophylactic efficacy of V920 and the durability of protective immunity as well as the immune correlates
- Study of the immunogenicity of V920 in NHP for up to 1-year post vaccination [PD003]

- Studies of the immunogenicity and efficacy of V920 in NHP conducted at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) [PD001, PD002, PD004]
- Study of the immunogenicity of a low dose of V920 [PD006]

Two additional studies were conducted to support the environmental risk assessment:

- Assessment of the ability of V920 to replicate in arthropod cell cultures of relevant vector species and in relevant vector species [PD007]
- Evaluation of the infectivity and potential for transmission of V920 in swine [PD008]

Vaccine lots used were assigned a potency value in plaque forming units (pfu) using the same non-validated potency assay that was used for release of clinical supplies. Clinical lots were used for most studies.

Table 2. Overview of studies performed by USAMRIID and by the applicant with V920

Study No.	Study type	Testing Facility	Species	No. per Group	Dose Regimen vaccination	Challenge	Assays	Findings
PD001 – V920	NHP Efficacy and Correlates of Protection by V920	USAMRIID ¹	Cynomolgus macaques (Cambodian origin)	8 per treatment group; 3 control animals (27 total animals)	one dose of 1 mL on Day 0; IM: 3×10^6 , 2×10^7 , or 1×10^8 pfu	IM challenge on Day 42; actual dose 358 pfu ²	Research grade ELISA Research grade PsVNA, qRT-PCR validated USAMRIID	Immunogenicity demonstrated in all vaccinated animals, 96% overall survival against lethal ZEBOV challenge
PD002 – V920	Dose-De-escalation Evaluation V920 immunogenicity and efficacy	USAMRIID	Cynomolgus macaques (Cambodian origin)	4 to 5 per treatment group; 2 control animals (24 total animals)	one dose of 1 mL on Day 0; IM: 3×10^2 , 3×10^3 , 3×10^4 , 3×10^5 , or 3×10^6 pfu	IM challenge on Day 42, month 3 or month 12, actual dose 645 pfu	interim report Research grade ELISA Research grade PsVNA (final report when data from qualified assays (Q2 solutions) available; qRT-PCR validated USAMRIID	Immunogenicity demonstrated in all vaccinated animals (ELISA for all animals, PsVNA for 6 vaccinated and 2 control animals), 100% overall survival against lethal ZEBOV challenge
PD003 – V920	Evaluation of the Durability of Protection from a Single Administration of V920 in Protection of Ebola Virus Challenged Cynomolgus Macaques	Merck Research Laboratories ³ (immunization phase)	Cynomolgus macaques (Mauritian origin)	1y cohort n=17; 3m cohort n=10; 42d cohort n=10 + 2 CTRL	one dose of 1 mL on Day 0; IM: 3×10^2 , 3×10^3 , 3×10^4 , 3×10^6 pfu (n=4/5) in 12 month cohort) or 3×10^6 pfu (all remaining NHP)	IM challenge on Day 42, month 3 or month 12, actual dose 357 pfu	Research grade ELISA Research grade PsVNA qRT-PCR validated USAMRIID; validated assays for ELISA and PsVNA outside protocol	Immunogenicity demonstrated in all vaccinated animals (those that were selected for challenge), survival against lethal IM ZEBOV challenge was 100% on day 42,
PD004 – V920		USAMRIID (challenge phase)		selection for challenge of 4 to 7 per cohort; 2 control animals				

				(19 total animals)				33% at 3 mo. and 43% at 12 mo.
PD006-V920	Evaluation of the Immunogenicity of Low Dose V920 in Cynomolgus Monkeys	Merck Research Laboratories	Cynomolgus macaques (Mauritian origin)	5 per treatment group	one dose of 1 mL on Day 0; IM: 30 or 2×10 ⁷ pfu; one dose of 1 mL on day 42, IM, 2×10 ⁷ pfu	NA	qualified ELISA conducted by Battelle Memorial Institute; qualified PRNT60 assay conducted at Q2 Solutions	Immunogenicity demonstrated in all vaccinated animals

All studies were performed under non-GLP conditions.

GLP = Good Laboratory Practice; IM = intramuscular; mL = millilitre; mo. = months; No. = number; pfu = plaque-forming unit(s)

¹ United States Army Medical Research Institute for Infectious Diseases (USAMRIID), Ft. Detrick, Maryland, USA

² Challenge dose used in all studies is 1000 pfu (nominal dose)

³ Merck Research Laboratories, West Point, Pennsylvania, USA; New Iberia Research Centre, New Iberia, Louisiana, USA

Primary pharmacodynamic studies

The primary pharmacodynamics properties of V920 were evaluated in several non-GLP immunogenicity and efficacy studies in NHP for which study reports were submitted, and further supported by literature data that, besides NHP, also concern rodents.

In studies conducted at USAMRIID and MSD, intramuscular administration of V920 vaccine was well tolerated and highly immunogenic in cynomolgus macaques across a wide dose range (3×10^1 to 1×10^8 pfu). These studies support immunogenicity of the vaccine, with ZEBOV-GP-specific IgG detectable in most animals 14 days after a single immunization with all animals seroconverting within 28 days. Protective efficacy against EVD was demonstrated, with 95 to 100% protection against mortality following a lethal intramuscular ZEBOV challenge 42 days after immunization.

Previously published studies demonstrated that a single immunization with V920 is highly immunogenic and effective in protection against disease and death by the lethal IM ZEBOV challenge in the NHP animal model. Notably, complete protection in NHP was observed as early as 7 days after a single vaccination, and partial protection at 3 days post vaccination, demonstrating a rapidly acquired protective immunity, which is of interest in the context of the use of V920 in outbreak settings.

Current NHP challenge models are more stringent than EVD in humans: a challenge dose of 1,000 pfu results in 100% lethality in unvaccinated cynomolgus macaques, and is generally thought to represent 100 to 1,000-fold Lethal Dose. In these conditions, and with survival as the most important endpoint, it can be concluded that V920 has shown to be protective in this model.

However, the high vaccine efficacy has hampered the identification of a potential correlate of protection. The aim of the studies to identify immune parameters that correlate with protection was not reached. On the other hand, many of the data of the planned assessment of the immune response were not available at the start of the procedure. These include the assessment of binding and neutralizing antibody titres in the qualified ELISA and PRNT60 assays but also experimental parameters such as T and B cell EliSpots, ICS, ADCC assay, Fc effector function assay etc. In addition, immune responses were sometimes only assessed for a selection of animals. In this regard, the currently ongoing efforts to obtain these data are strongly supported and are expected to provide some new insight into the immune correlate of protection. During review of the MAA, 3 study reports were submitted on the assessment of binding and neutralizing antibody titres in the qualified ELISA and PRNT assays. The Applicant clarified that the experimental parameters as identified above are no longer seen as a priority. Focus is currently on the assessment of Fc effector functions. In addition, outcomes other than survival will also be evaluated (viremia, clinical signs). Submission of these upcoming data for review is considered important in the post-authorisation phase.

The important role of humoral immune response in protection has been substantiated by depletion studies in NHP as described in the literature. It has been demonstrated that absence of antibodies (due to depletion of CD4 T cells at the time of vaccination) leads to death after challenge, whereas animals survive when CD4 T cells are depleted at the time of challenge, as do animals depleted of CD8 cells at the time of vaccination. Altogether these data show the importance of a humoral immune response upon vaccination. CD4 T cells also play an important role in protection, as indicated by depletion assays as well as outcome of SHIV infected animals, but rather to provide help to B cells than via CD4 T cell effector functions. Still, confirmatory data with respect to the exact role of T-cell immunity vs. antibodies are missing.

Assessment of endpoints other than mortality could provide additional information from the performed studies. So far, these studies indicate that no sterile immunity is obtained by vaccination. Indeed, a number of vaccinated animals that survived had detectable viremia after challenge, and some also had

clinical signs indicative of infection (although no histologic lesions of Ebola viral infection were observed). Viremia after challenge was higher in the durability study (PD004), as compared to previous challenge studies performed by USAMRIID, and animal source (Mauritian versus Cambodian) or external factors like stress related to long transportation may have influenced this parameter. Viremia could be an interesting parameter as alternative to survival for assessment of correlates of protection. The Applicant will further evaluate long term protection in an ongoing and planned durability study to be submitted post-authorisation.

To date, the exact duration of protection after a single dose of V920 is not fully understood. In the durability study in NHP (PD004), robust antibody titres but only partial protection against IM challenge were observed at three months (33% survival) and 1 year (43% survival) after a single vaccination. Some caveats in this study make it difficult to determine the meaning of these data, including the different origin of the cynomolgus macaques compared to previous NHP studies (Mauritian versus Cambodian origin) and that the animals underwent long-distance transportation one week prior to challenge. Also for this study immunogenicity assessment with validated assays and additional immune parameters is ongoing. Overall, data on duration of protection are considered limited at this time, as corresponding human data are not available either.

In any case, the fact that protection long term is reduced despite the presence of circulating antibodies raises concerns on what could be the best biomarker for determining long term protection. The adequacy of the current stringent NHP model for long term protection may deserve discussion as well.

Safety pharmacology programme

No stand-alone safety pharmacology study has been conducted, in the light of results of the nonclinical general toxicity studies and clinical safety, as per the applicable regulatory guidelines.

2.3.3. Pharmacokinetics

No pharmacokinetics studies have been conducted for V920. This is consistent with WHO Guidelines on nonclinical evaluation of vaccines (2005) which indicates that pharmacokinetic studies (e.g. for determining serum or tissue concentrations of vaccine components) are not needed for vaccines. Results of distribution, persistence and shedding studies are discussed in the toxicology section.

2.3.4. Toxicology

Several exploratory efficacy and/or immunogenicity studies conducted with V920 in BALB/c mouse, Sprague Dawley rat and cynomolgus macaque demonstrated robust immunogenicity following single or multiple intramuscular injections supporting the use of these species for the pivotal toxicity studies. All toxicity studies were GLP compliant except for the exploratory immunogenicity and viremia study in rats and the neurovirulence study. Clinical drug product was used in all these studies except for the neurovirulence study, which was performed with research grade material.

The V920 vaccine virus showed approximately 33% slower growth kinetics than wild-type VSV in Vero cell cultures, contributing to attenuation.

Repeat dose toxicity

Repeat dose toxicity studies were conducted in two species, mice and monkeys. Animals received 2 doses of the vaccine, one more than the clinical dose regimen (single dose). Doses up to 2×10^7 pfu in mice or 1×10^8 pfu in cynomolgus macaques were found to be safe and well-tolerated. Findings are in line with what can be expected from an immunogenic vaccine, with immune stimulation (lymphoid expansion in

local lymph nodes and spleen) and mild local irritation and inflammation. The NOAELs are agreed to be the highest dose tested, corresponding to a dose in the same order of magnitude as a clinical dose. Study design including species selection, number of doses, dose, assessment of recovery was in line with relevant guidelines and is considered acceptable.

Genotoxicity and carcinogenicity

The absence of genotoxicity and carcinogenicity studies is considered acceptable based on current guidelines and given the type of product and its posology.

Reproduction Toxicity

The developmental and reproductive toxicology study in Sprague Dawley rats was designed taking into account the recommendations of the WHO guidelines on nonclinical evaluations of vaccines, regarding pre-mating treatment to ensure exposure and induction of immune response leading to antibody transfer (5.28×10^7 pfu, given 28 and 7 days prior to cohabitation, on gestation day 6 and on lactation day 7), and a second group to evaluate viremia (single dose of 5.28×10^7 pfu on GD6), a dose comparable to a full human dose, same route of administration as intended for human use, evaluated endpoints and division in subgroups (caesarean / postnatal follow-up). Although the classical way for calculation of safety margins may not be that relevant for a live vaccine, large body weight based safety margins, together with observed immune response and viremia in the immunogenicity and viremia group respectively, support the Applicant's conclusion that vaccination before and during gestation is well tolerated under the conditions of this study, with no effect on mating or pre- and post-natal development and no teratogenic potential. When V920 was administered to female rats, antibodies against ZEBOV GP were detected in foetuses and offspring, likely due to trans-placental transfer during gestation and with the acquisition of maternal antibodies during lactation, respectively.

Toxicokinetic data

V920 is a live attenuated vaccine and as such, its distribution, persistence and shedding were evaluated in cynomolgus monkeys after IM administration. The biodistribution study showed persistence of V920 viral RNA (by qRT-PCR) in lymphoid tissues but no evidence for persistence of infectious virus (by plaque assay). Viral RNA after Day 7 was generally confined to tissues lacking potential for shedding in excretions or secretions and showed no evidence of distribution to the brain or spinal cord at any time point. It should be noted that in clinical trials, positive saliva samples were detected and in repeat dose toxicity studies, urine samples were positive for some animals (mice and NHP). Dissemination to the environment or transmission from vaccinees to close contacts can therefore not be excluded. As samples were only assessed for presence of infectious virus vaccine at limited timepoints, it is not known how long the infectious virus was present for. At day one, several samples were positive and at day 56, all were negative but no intermediate timepoints were assessed. The Applicant hypothesized that the vaccine RNA detected in lymphoid tissues beyond d56 results from viral genomic RNA within macrophages trafficked to the lymphoid tissues, which is supported by literature (Simon et al., 2007, 2010). The lack of detectable long-term VSV vaccine vector replication *in vivo* minimizes concerns about accumulation of mutations in live-attenuated vectors that could potentially lead to increased vector virulence.

Local Tolerance

Local tolerance was assessed in the repeat dose toxicity studies in line with the current guidelines.

Other toxicity studies

An exploratory neurovirulence study was conducted with V920 in cynomolgus macaques demonstrating no evidence of neurovirulence following intrathalamic administration (Mire et al, 2012). These results, together with the results of the biodistribution study described above showing absence of vaccine genetic material in CNS tissues, show that there is no tropism for the CNS, and even if the vaccine virus is introduced intrathalamically in the CNS of NHP, no neurological symptoms are observed. Hence, these data support the use of the vaccine in the proposed indication and population.

rd-rHSA is a novel excipient, and should, as such, be subject to a specific safety assessment, and toxicology and PK should be investigated. The applicant provided a justification as to why additional nonclinical studies are not needed. Rice-derived recombinant and plasma-derived HSA are identical, and considering pd-HSA is a qualified excipient, the only potential safety concern consists in the fact that rice host cell proteins might theoretically induce a risk of allergic reactions. However additional nonclinical studies would not be able to fully exclude this theoretical risk. Therefore, it is agreed that no additional nonclinical studies are warranted to validate the excipient in the proposed formulation and use.

2.3.5. Ecotoxicity/environmental risk assessment

V920 is a live attenuated vaccine carrying a single-stranded negative sense RNA genome. The vaccine consists of a recombinant vesicular stomatitis virus (rVSV) in which the gene encoding the VSV glycoprotein G has been replaced with the Zaire Ebola virus (ZEBOV) glycoprotein (GP).

Data collected from clinical trials with V920 show that viremia (measured by the detection of rVSVΔG-ZEBOV-GP RNA in the blood) was common among vaccine recipients, with a maximum viremia value observed of 2.9×10^4 copies/mL. Viremia resolved in most subjects by 1 week (see also section 2.6 page 106). Shedding of the V920 virus (measured by the detection of rVSVΔG-ZEBOV-GP RNA in saliva, urine, and fluid from skin vesicles) was rare in adults. Adolescents and children presented a higher magnitude of vaccine viremia and a greater degree of vaccine viral shedding in the saliva and urine compared to adults (maximum shedding observed was 7×10^4 copies/mL in adolescent saliva).

Person-to-person transmission of the V920 virus has not been documented. Because shedding data indicate the presence of V920 in bodily fluids and in vesicular lesions and because the cell tropism of rVSVΔG-ZEBOV-GP show features consistent with both VSV and ZEBOV, the dissemination of V920 in human population by vaccinees cannot be ruled out. V920 seems generally well tolerated though systemic and local adverse effects have been reported, with amongst others the possibility for vesicular rash or cutaneous vasculitis following vaccination by means of which exposure to V920 is possible. Very limited information is available on the safety of V920 in vulnerable populations such as immune compromised, pregnant or lactating women or children below 1 year of age.

Because this vaccine is based on VSV, a known pathogen in livestock (e.g. horses, cattle, pigs), the risk assessment included species that are relevant for the wild type VSV backbone of this vaccine. Virulence or replication of V920 has been investigated in rodents, pigs, swine, arthropods and non-human primates. In pigs, viremia and clinical signs consistent with wt-VSV were observed, albeit with delayed appearance compared to the wild-type VSV infection. No transmission to control animals was detected. The possibility of recombination events between the vaccine vector and wt-VSV was evaluated and is considered very low.

Upon request, the applicant provided additional information for vaccine recipients and medical centre to ensure optimal and effective implementation of the proposed risk management measures. As a precaution, vaccinees should attempt to avoid exposure of livestock to blood and bodily fluids for at least 6 weeks following vaccination to avoid the theoretical risk of spread of the V920 vaccine virus. People who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal. Cover the

vaccination site with an adequate bandage (e.g. any adhesive bandage or gauze and tape) that provides a physical barrier to protect against direct contact with vesicle fluid. The bandage may be removed when there is no visible fluid leakage. To avoid unintended exposure to livestock, ensure medical waste and other cleaning materials do not come in contact with livestock.

Based on limited shedding in adults, the results of a toxicity study in non-human primates, and lack of horizontal transmission in pigs, the overall risk of Ervebo to human health and the environment is considered negligible.

In any case, any unused vaccine or waste material should be disposed in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

2.3.6. Discussion on non-clinical aspects

The results from pharmacology studies conducted with V920 by USAMRIID and MSD, and supported by literature data, demonstrate immunogenicity of the vaccine and protective efficacy against EVD following intramuscular ZEBOV challenge 42 days after immunization. Still less well understood is how long the protection conferred by a single IM dose of V920 can last and what the specific mechanism for protection would be. No major objections were identified, and no additional studies are required. Overall, antibody responses upon vaccination are robust but it is not possible that a threshold of antibody titre predicting survival or time of death can be identified at the present time. This conclusion is supported by the final analysis of the immunogenicity data from study PD001, PD002, PD003 and PD004, as the missing long-term immunogenicity data on animals that were vaccinated but not selected for challenge were submitted during the procedure (PD003-PD004). Immune correlates of protection will be further explored, including assessment of antibody titre correlates to outcomes other than survival, such as EBOV titre and clinical score post challenge, and time to death in the durability study where survival was much less than 100%. These results will be provided post-authorisation.

Besides efforts to explore correlation of available immune response parameters, ELISA and PRNT titres, to outcomes other than survival, data will also be generated on other antibody features than titre and neutralisation, including Fc effector function, isotype and antibody specificity. These data will be explored in the durability study, PD004, which is appropriate as some vaccinated animals succumbed in this study and other parameters (viremia after challenge, clinical score, time to death) can be assessed as well. Depending on the outcome of this analysis, it will be considered if conducting similar analysis for the other studies is relevant. The assessment of those parameters that are identified in the protocols as experimental parameters, including T and B cell Elispots, ICS, and ADCC assay have not been done, and are not planned in the near future. This can be considered acceptable in view of ongoing efforts to explore other immune correlates as indicated above.

Durability data are considered limited, as human durability data are not available either. Further assessment of the immune response in the durability study is ongoing, and to better interpret the data regarding duration of protection, submission for review of these data post-authorisation is considered important. In addition, following this 1-year durability study and the difficulties encountered for interpretation of the data, the Applicant is in the process of generating more durability data in an ongoing (4 month) and planned (1 year) durability study. Current data show however reduced protection.

Pharmacokinetic studies are normally not required for a vaccine. The applicant provides a distribution, persistence and shedding study in monkeys but no other toxicokinetics studies were performed with V920 vaccine, which is acceptable.

All pivotal toxicology studies have been conducted according to GLP requirements and the relevant EMA and WHO guidelines. Safety has been assessed in repeat dose toxicity studies in mice and non-human primates, in a reproductive and developmental toxicity study in rats, and an exploratory neurovirulence

study in non-human primates. Overall the pivotal toxicity studies have adequate design and conduct, and results do not raise any safety signal of concern.

In addition, the neurovirulence study with V920 was non-GLP, which was undesirable. However, at this stage, this is a non-issue because the clinical safety database gathered to date does not show signals of major safety concern, and a GLP-compliant biodistribution study in NHP did not show evidence of V920 distribution to the brain. Accordingly, re-testing of neurovirulence for V920 under the GLP conditions is deemed unnecessary.

The GMO ERA concludes that the overall risk linked to the intended use of V920 for both humans and the environment is considered negligible.

Overall, the nonclinical safety data demonstrate that V920 has an acceptable safety profile.

2.3.7. Conclusion on the non-clinical aspects

Collectively, the results from pharmacology studies conducted with V920 by USAMRIID and MSD, and supported by literature data, demonstrate protection after challenge and induction of a robust immune response. Also considering the clinical data indicative of vaccine efficacy, the provided nonclinical pharmacology data are considered sufficient to support the use of V920 in individuals at high risk of exposure in the short term, e.g. in an outbreak setting.

Data originated from distribution, persistence and shedding studies in monkeys showed no major concerns.

The toxicity profile of V920 has been thoroughly evaluated and the nonclinical data support the acceptable safety profile of V920 as a vaccine that could be used for active immunization of at-risk individuals to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.

From a non-clinical point of view, this marketing authorisation application is approvable.

Recommendations for future non-clinical development

- Results from ongoing investigations of immune correlates of protection to outcomes other than survival, concerning studies PD001, PD002 and PD004, should be submitted once available.
- For the durability study PD004, the report on immunogenicity data generated by the validated ELISA and PRNT assays should be submitted once available. The results of the ongoing assessment of additional immune parameters (Fc effector function, isotype and antibody specificity) should be submitted once available.
- Data from ongoing and planned durability studies #AP-17-040W and #AP-17-040W2 should be submitted once available.
- (GMO-ERA) The applicant should submit further information on the LOD and LOQ in the context of post-approval variation application.

2.4. Clinical aspects

2.4.1. Introduction

The V920 clinical program was initiated in response to the 2014-2016 Ebola outbreak which was declared a PHEIC (Public Health Emergency of International Concern) by WHO in August 2014. Several international organisations were involved as partners, including WHO, the Center for Disease Control and

Prevention, Médecins Sans Frontières, the National Institutes of Health, the Biomedical Advanced Research and Development Authority, the Walter Reed Army Institute of Research, the Joint Vaccine Acquisition Program, the Public Health Agency of Canada, the Defense Threat Reduction Agency, NewLink Genetics (Bio-Protection Systems Corporation), and various Ministries of Health.

The application includes a total of twelve studies: 8 Phase I trials (sponsors: MSD, University Hospitals of Geneva, Universitätsklinikum Hamburg-Eppendorf, Universitätsklinikum Tübingen, University of Oxford, Dalhousie University, IWK health centre, Wellcome trust), 2 Phase II trials (sponsors: CDC or NIAID, NIH and others) and 2 Phase III trials (sponsors: WHO or MSD).

Several other studies are ongoing, and the results will be submitted post-licensure.

V920 is also being deployed in the ongoing Ebola outbreak in the DRC under an expanded access protocol through which effectiveness and safety data are being collected.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3. Overview of Clinical Trials included in the V920 application

Protocol Number	Phase	Country	Trial Design	V920 Dosing Regimen* and Exposure (n)	Trial Population	Trial Endpoints	Type of Data Presented
V920-001 (NLG 0307; WRAIR 2163)	1	United States	Randomized, single-center, double-blind, placebo-controlled, dose-escalation	3 × 10 ⁶ pfu (n=10), 2 × 10 ⁷ pfu (n=10), 1 × 10 ⁸ pfu (n=10), placebo (n=9)	Healthy eligible subjects between the ages of 18 and 50 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-002 (NLG 0207; NIH 15-I-0001)	1	United States	Randomized, single-center, double-blind, placebo controlled, dose-escalation	3 × 10 ⁶ pfu (n=10), 2 × 10 ⁷ pfu (n=10), 1 × 10 ⁸ pfu (n=10), placebo (n=9) on Days 0 and 28	Healthy eligible subjects between the ages of 18 and 65 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-003 (#C11401, Halifax, Canada)	1	Canada	Randomized, single-center, double-blind, placebo controlled, dose-ranging	1 × 10 ⁵ pfu (n=10), 5 × 10 ⁵ pfu (n=10), 3 × 10 ⁶ pfu (n=10), placebo (n=10)	Healthy eligible subjects between the ages of 18 and 65 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-004 (NLG 0507)	1b	United States	Randomized, multi-center, double-blind, placebo controlled, dose-response	3 × 10 ³ pfu (n=64), 3 × 10 ⁴ pfu (n=64), 3 × 10 ⁵ pfu (n=64), 3 × 10 ⁶ pfu (n=84), 9 × 10 ⁶ pfu (n=47), 2 × 10 ⁷ pfu (n=47), 1 × 10 ⁸ pfu (n=48), placebo (n=94)	Healthy eligible subjects between the ages of 18 and 60 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PRNT assays)
V920-005	1	Switzerland	Randomized, single-center, double-blind, placebo-controlled, dose-finding	3 × 10 ⁵ pfu (n=51), 1 × 10 ⁷ pfu (n=35), 5 × 10 ⁷ pfu (n=16), placebo (n=13)	Healthy eligible subjects between the ages of 18 and 65 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-006	1	Germany	Open label, single-center, dose escalation	3 × 10 ⁵ pfu (n=10), 3 × 10 ⁶ pfu (n=10), 2 × 10 ⁷ pfu (n=10)	Healthy eligible subjects between the ages of 18 and 55 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)

Protocol Number	Phase	Country	Trial Design*	V920 Dosing Regimen* and Exposure (n)	Trial Population	Trial Endpoints	Type of Data Presented
V920-007	1	Gabon	Open label, single-center, dose escalation	3 × 10 ³ pfu (n=20), 3 × 10 ⁴ pfu (n=19), 3 × 10 ⁵ pfu (n=20), 3 × 10 ⁶ pfu (n=39), 2 × 10 ⁷ pfu (n=16), 2 × 10 ⁷ pfu, 6 to 12 years (n=20), 2 × 10 ⁷ pfu, 13 to 17 years (n=20)	Healthy eligible subjects between the ages of 18 and 50 years as well as children ages 6 to 17 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-008	1	Kenya	Open label, single-center, dose escalation	3 × 10 ⁶ pfu (n=20), 2 × 10 ⁷ pfu (n=20)	Healthy eligible adult health workers ages 18 to 55 years	Safety and immunogenicity	Immunogenicity data (non-validated ELISA and PsVNA assays)
V920-009	2	Liberia	Randomized, single-center, double-blind, placebo-controlled	2 × 10 ⁷ pfu (n=500), placebo (n=500)	Subjects ≥18 years	Safety and immunogenicity	Immunogenicity data (validated GP-ELISA and PRNT)
V920-010	3	Guinea	Open-label, cluster-randomized, controlled, ring vaccination	2 × 10 ⁷ pfu <u>Randomized Subjects</u> Immediate Vaccination: n=2119 Delayed Vaccination: n=2041 <u>Non-randomized Subjects</u> Immediate Vaccination: n=1677 (included n=194 subjects 6 to <18 years of age)	Subjects ≥18 years of age who live in the defined vaccination ring Children and adolescents 6 to <18 years of age	Efficacy and safety	Efficacy data
V920-011	2/3	Sierra Leone	Randomized, multi-center, open-label	2 × 10 ⁷ pfu, Immediate Vaccination: 4165 Deferred Vaccination: 12 ¹ Deferred Vaccination Crossover: 3821	Subjects ≥18 years who are at high risk of exposure to EVD	Safety and immunogenicity	Immunogenicity data (validated GP-ELISA and PRNT)
V920-012	3	United States, Canada, Spain	Randomized, multi-center, double-blind, placebo-controlled	2 × 10 ⁷ pfu (n=266), 2 × 10 ⁷ pfu (n=265), 2 × 10 ⁷ pfu (n=266), 1 × 10 ⁸ pfu (n=264), placebo (n=133)	Healthy eligible subjects between the ages of 18 and 65 years	Safety and immunogenicity (lot consistency)	Immunogenicity data (validated GP-ELISA and PRNT)

Table 4. Overview of ongoing or planned clinical trials or clinical protocols

Study	Phase	Design	Objective	Subjects	Country	Status
Ongoing or planned clinical trials						
V920-013	2	Randomised, open label, booster	Immuno PREP	≥ 18 YOA potential occupational risk	US, Canada	ongoing
V920-015	2	RCT, double blind	Safety/immuno in HIV+, 1 or 2 doses	HIV+	Canada, Burkina Faso, Senegal	ongoing
V920-016 (PREVAC)	2	RCT, double blind	Compare 3 vaccines strategies (J&J, V920, V920+boost)	≥ 1 YOA children and adults	Guinea, Liberia, Sierr Leone, Mali	ongoing
V920-017	3b	Open label, non randomised ring	Expanded access if additional outbreak, safety effectiveness	≥ 6 YOA	Uganda, Guinea B., Mali, IC, BF, Nigeria, DRC, Niger, Gabon	planned
V920-018	3	Randomised (Guinea FLW)	Efficacy/safety CoP analysis	frontline workers	Guinea	Completed; Clinical Study Report in preparation
Emergency use clinical protocols						
Expanded access	NA	Open label cohort study		≥ 6 YOA with possible delayed transmission	Guinea	Started Oct. 2015

				by survivors		
Expanded access	NA	RCT, PREVAIL	CHAd3 (GSK) vs V920 (MSD)	≥18 YOA at risk for Ebola infection	Liberia	Completed
Expanded access	NA	Open label, non randomised ring		≥6 YOA	Guinea, Liberia	Completed
Expanded access	NA	Open label, non randomised ring		≥1 YOA	DRC	Started May 2018
Expanded access	NA	Open label, non randomised ring		≥1 YOA	DRC, North Kivu	Started Aug. 2018

2.4.2. Pharmacokinetics

No clinical pharmacology studies describing the pharmacokinetic properties of V920 were conducted in support of this application. This is acceptable because pharmacokinetic studies are generally not required for vaccines because the kinetic properties of antigens do not provide useful information for determining dose recommendations according to the "Note for guidance on the clinical evaluation of vaccines" CHMP/VWP/164653/2005.

The main characteristics of the *in vivo* behaviour of the live V920 vaccine virus have been evaluated through assessment of vaccine viremia and shedding. Vaccine viremia (defined as the presence of vaccine viruses in the blood stream) and shedding were investigated as a safety parameter, but also as a measure of the bioavailability and replicative ability of the vaccine virus. Virus shedding was determined by the presence of the vaccine viruses in secretion or excretion products, and it was assessed in urine and saliva (phase I trials) but also in liquid of vesicles and in synovial fluids (phase II and III studies).

Viremia and shedding were measured using a RT-PCR assay in the 8 Phase I studies at different time points (from Day 1 to Day 84 depending on the study) and occasionally in the Phase 2/3 studies.

Vaccine viremia

Vaccine viremia was evaluated in 771 adult subjects vaccinated with V920 dose levels ranging from 3×10^3 to 1×10^8 pfu. 186 adult subjects were vaccinated with the selected dose of 2×10^7 pfu (n=110) or higher (n=76).

V920 vaccine virus was detectable in the plasma of most adult subjects vaccinated with vaccine doses $\geq 1 \times 10^5$ pfu and mainly from Day 1 to Day 7. At the following time point, by Day 14, viremia was no longer detected except for one subject (although it was not tested for all subjects).

School-age children and adolescents vaccinated with the dose level of 2×10^7 pfu were viremic from Day 1 to Day 7 and copy numbers/ml were in the same range as those of adults. Vaccine viremia has not been investigated more than 7 days post-vaccination in this paediatric population.

Viral shedding

Shedding was detected by PCR in urine or saliva in 23 adult subjects out of 299 vaccinated subjects who had samples collected and tested. Shedding in urine was observed from Day 1 through Day 7. Shedding in saliva was observed from Day 1 through Day 14 after any dose level.

Vaccine virus was also detected in skin vesicles of 4 adult subjects out of 10 subjects tested in the V920-005 trial. Virus RNA was detected in a skin vesicle at 12 days postvaccination in one of the four subjects.

Virus shedding was detected in a higher proportion of school-age children and adolescents (28/39) (V920-007 study) compared to adults. At Day 7, V920 RNA was detectable in saliva in 35% of school-age children and in 88% of adolescents, and in a urine sample from 1 school-age child.

Discussion and conclusion on viremia and viral shedding

Vaccine virus RNA was found in blood, saliva and urine of vaccinated adults, although at low incidence and low copy number using RT-PCR. V920 RNA was detected in liquids of vesicles. Since WT EBOV RNA has been detected in other biological fluids than urine and saliva such as the semen, vaginal fluids, aqueous humour, breast milk, faeces, sweat, amniotic fluid and placenta, V920 virus might also be present in such fluids although it is unknown for which duration.

No infectious assays were performed to distinguish between circulating or shed virus and infectious particles. Therefore, it remains difficult to clearly define the risk associated to viremia and shedding.

The kinetics of viral clearance also remains uncertain. It is however unlikely that live viruses persist in the blood or bodily fluids of a vaccinated adult more than 28 days post-vaccination.

Based on the results discussed there is a theoretical risk of transmission of V920 from human-to-human and a potential related safety issue, particularly for high-risk individuals.

The risk of transmission to high-risk individuals is addressed in the section 4.4 of the SmPC. Vaccine recipients should avoid close association with and exposure of high-risk individuals to blood and bodily fluids for at least 6 weeks following vaccination. Blood donation should be avoided for at least 6 weeks post-vaccination. Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal to minimize the risk of possible transmission of the vaccine virus through open vesicles. The theoretical possible transmission of V920 to livestock is also mentioned in section 4.4 for this reason.

As a precautionary measure, it is preferable to avoid the use of Ervebo during pregnancy. The benefit of breast-feeding for the child and the benefit of vaccination for the mother should be balanced.

A warning that the 'use of other Ebola control measures' should not be interrupted after vaccination was included in the section 4.4 of the SmPC as well as 'Standard precautions when caring for patients with known or suspected Ebola disease'. Warnings and precautions on how to protect themselves and how to avoid spread of germs were also implemented in the PL.

Vaccine viremia and shedding were more pronounced in school-age children and adolescents. The duration of viremia and shedding in children and adolescent is not known. No data on viremia and shedding were presented for HIV-seropositive subjects, pregnant woman or elderly subjects (>65 YOA). Viral shedding will be further characterized in ongoing V920-015 ACHIV and V920-016 PREVAC studies, respectively investigating HIV-infected adults and adolescent and healthy adults and children.

Finally, since the release specifications are based on the vaccine lots used in the clinical trials, the commercial lots are expected to have similar viremia and shedding.

2.4.3. Pharmacodynamics (Immunogenicity data)

Mechanism of action

V920 consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope glycoprotein gene of Zaire Ebola virus (rVSVΔG-ZEBOV-GP). Protective immunity against Ebola virus is not well understood and continues to be explored in animal models and clinical trials. Ebola virus GP is the major antigen in the vaccine and has been shown to induce virus-neutralizing antibodies as well as non-neutralizing antibodies.

There is currently no established immunological correlate of protection against ZEBOV. The relative contributions of innate, humoral and cell-mediated immunity to protection from Zaire Ebola virus are unknown.

Clinical Immunogenicity

The pharmacodynamic profile for the V920 Ebola vaccine is the interaction with the immune system aiming at the induction of an immune response. Thus, the immunogenicity of V920 Ebola vaccine is described in this section.

The clinical development program of V920 consists of 12 clinical trials with immunogenicity data available for 11 of them. No immunogenicity data are available for the efficacy part of the pivotal V920-010 trial. A total of 15,997 adult subjects were vaccinated with V920 in these clinical trials; 15,399 of these subjects received 2×10^7 plaque forming units (pfu)/dose or higher of V920. The trials also included approximately 536 adults ≥ 65 years of age, 234 children 6 to 17 years of age, 278 women who were incidentally found to be pregnant during the clinical trials, and 22 HIV-positive individuals (in the V920-009 trial only).

Assays used to evaluate immunogenicity

Immune responses to V920 were evaluated by 2 types of assays in the program, GP-ELISA and virus neutralization assays (Pseudovirion neutralization assay [PsVNA] and Plaque Reduction Neutralization Test [PRNT]).

The GP-ELISA measures total IgG binding antibodies against the Ebola GP. It is an indirect ELISA which utilizes a purified recombinant GP as the coating antigen and an enzyme-conjugated anti-human IgG secondary antibody as the reporter or signal system. Testing was conducted at different laboratories during development. The PsVNA and PRNT detect the virus neutralizing antibody levels from human sera following the administration of the V920 vaccine.

In the 8 Phase 1 trials, non-validated GP-ELISA, PsVNA, and PRNT assays were utilized to assess immunogenicity. Testing was done in different laboratories. Validated GP-ELISA (FANG human ZEBOV-GP ELISA) and PRNT results were presented for the Phase 2 and 3 studies V920-009, V920-011, and V920-012. Virus neutralization was measured by PsVNA in 7 of the Phase 1 trials; the exception was V920-004, in which, virus neutralization was measured by PRNT. The validation reports for the GP-ELISA assay and PRNT were approved by the FDA in February 2017. Validation protocol and reports, including the performance of the ELISA, particularly in term of reproducibility, sensitivity and specificity, were evaluated and deemed acceptable. To enhance the analysis, a serostatus cut-off (SSCO) is applied which is endorsed (see also below).

ELISA titres were expressed in Units/ml, endpoint titres or EC90 in the initial Phase 1 studies; subsequently the ZEBOV-GP ELISA titres expressed in ELISA Units (EU)/ml were further defined as the primary immunologic endpoint for the V920 program. The lower limit of quantification (LLOQ) was 58.84.

The immunogenicity analyses included the assessment of the geometric mean titre (GMT), geometric mean fold rise (GMFR), and seroresponse in the GP-ELISA and the PRNT assays. Seroresponse definitions were different for the Phase 1 studies compared to the Phase 2 and 3 studies because the cut-off of seropositivity and the seroresponse criteria were determined after having obtained the immunogenicity results of the Phase 1 and the PREVAIL studies. The rationale for the choice of the selected serostatus cut-off of 200 EU/ml was to decrease the proportion of pre-vaccination positive subjects compared to the use of the assay LLOQ in a non-endemic population. The choice of the cut-off is endorsed. An assessment of immunogenicity based on the baseline Ab status is being conducted and the applicant will provide the data and the results of the immunogenicity evaluation post-authorisation.

Similarly, seroconversion/seroresponse criteria were arbitrarily defined. Seroconversion was defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 4-fold increase in ZEBOV IgG compared with baseline (Phase 1, primary endpoint and Phase 2/3, secondary endpoint) and seroresponse was

defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 2-fold increase in ZEBOV IgG compared with baseline (Phase 2/3, primary endpoint). Results were described in term of seroconversion rate (SCR), proportion of subjects meeting seroresponse criteria at specific timepoints, and geometric mean concentration (GMT).

The PsVNA and PRNT are both neutralization assays to determine the virus neutralizing antibody levels from human sera after vaccination. However, PsVNA differs from the PRNT in that the *in vitro* pseudovirion can infect cells but cannot replicate. The PsVNA was replaced by the PRNT assay in the Phase 2 and 3 studies because of lack of validation due to technical limitations including variability of reagents. As mentioned above, the PRNT assay was further qualified and validated before its use in the Phase 2 and 3 studies. The PRNT validation results confirm the performance characteristics of the PRNT assay and demonstrate that the assay is suitable for its intended use.

PRNT based on 60% reduction in viral plaque was selected to measure Ab neutralization capacities. Data indicating whether Ab detected as neutralizing V920 are able to neutralize WT EBOV became available during the procedure (a panel of 7 samples from NIBSC has been tested at Focus Diagnostics and the Ab titres generated in the rVSV Δ G-ZEBOV-GP-based PRNT were compared with a wild-type neutralization assay). Results support the fact that Ab detected as neutralizing V920 are able to neutralize WT EBOV *in vitro*.

The clinical relevance of the PRNT assay is not known; considerations should be given as to whether virus neutralizing activity detected in an *in vitro* assay is predictive of EBOV neutralizing activity *in vivo*. To help further clarifying the clinical relevance of the immune response, the Applicant will provide analyses of immune correlates of protection post-authorisation.

Characterization of adaptive cellular response to vaccine antigen or peptides (B- and T-cell responses) was planned to be explored in various Phase 1 trials (V920 -001, -002, -003, -005, -006, -007) using various techniques such as EliSpot, flow cytometry or mass spectrometry. Vaccine-induced innate responses were also planned to be investigated. The results of the exploratory assays are not essential for defining the benefit/risk of V920 and thus it is acceptable that they will be provided by the Applicant as soon as available in the post-authorisation phase.

Some limited preliminary data on cross reacting binding or neutralizing antibody responses against related haemorrhagic fever viruses (e.g. Sudan ebolavirus) were presented by the Applicant; however, no conclusion could be drawn.

Gamma irradiation

The blood samples collected in the V920-009 and V920-011 trials (conducted in West Africa in the context of an ongoing Ebola outbreak) were gamma irradiated at the target dose of 50 kilograys (kGy) to inactivate Ebola virus, if present. After irradiation, these samples were tested in the validated GP-ELISA and PRNT. The blood samples collected in the V920-012 trial were not gamma-irradiated prior to testing in the validated assays because there was no risk that the specimens contained Ebola virus as the trial was conducted outside of the outbreak setting.

A gamma irradiation study was performed utilizing 60 samples from the American phase I trial (Protocol V920-004) and various control samples, which spanned the dynamic range of both the validated ELISA and qualified PRNT. In this study, gamma irradiation has been demonstrated to result in an approximate 20% elevation in measured antibody response for negative clinical samples. Conversely, gamma irradiation resulted in an approximate 20% reduction in post vaccination antibody response (1.21-fold decrease with 95% [CI = 1.15, 1.27-fold]) in the GP-ELISA. Reference standard (RS) and quality controls (QC) were not gamma irradiated. The effect of gamma irradiation was not consistently observed for the PRNT.

As consequence of the elevation in Day 0 and reduction in Day 56 concentration, the fold-change in response to vaccination (Day 56/Day 0) for the gamma irradiated samples as compared to the non-gamma irradiated samples correspond to a 42% reduction on average in the ELISA, meaning that the percentage of subjects achieving a 4-fold rise in response to vaccination could be reduced.

Gamma-irradiation was only one of the factors that influenced the choice of seroresponse criteria. As mentioned previously, the choice of the seroresponse criteria was mainly based on the Liberian PREVAIL study as representative of the target population.

A potential explanation for the effects of gamma irradiation is that irradiation partially denatures antibodies, causing nonspecific binding pre-vaccination in the GP-ELISA as well as decreased specific binding in the GP ELISA post-vaccination. Gamma irradiation was applied to the specimens from V920-009 and V920-011 clinical trials where lower GMTs for all time points have been observed.

Dose-response studies

Eight Phase I trials (V920-001 to V920-008) were conducted in the US and Canada, Europe (Switzerland and Germany), and regions of Africa not affected by the outbreak (Gabon and Kenya, V920-007 and V920-008) to evaluate the immunogenicity and safety of the V920 vaccine and to establish the final dose.

The Phase I dose finding program included 795 adult subjects who received V920 as a single dose ranging from 3×10^3 pfu/dose to 1×10^8 pfu/dose. The Phase I trials included 197 adult subjects who received a single dose of 2×10^7 pfu or higher of V920. The dose level of 2×10^7 pfu was evaluated in 40 children and adolescents (V920-007). Overall, 135 subjects received placebo in the Phase I blinded trials. All the trials administered a single IM dose of V920, except the V920-002 trial in which 2 doses were administered (prime-boost regimen). Immunogenicity was assessed at different time points (from Day 0 up to Day 365). Not all time points were evaluated in all phase I trials. Non-validated ELISA, PsVNA or PRNT were used to assess the immunogenicity of V920.

GMTs, GMFRs and seroconversion rates (SCRs) were evaluated. In all phase I trials, for ELISA antibody titres the seroconversion was defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 4-fold increase in ZEBOV IgG compared to baseline.

The results of the phase I trials allowed to assess the anti-GP antibody kinetics after vaccination. GMTs, GMFR, and SCRs were higher at all time points in the vaccine groups compared with the placebo groups, where no response was observed. No immune response was observed for any dose group on day 7 (EBOV-naïve subjects, studies V920-001 to V920-004). Antibody titres increased from day 7 and were measurable to a different extent in all dosing groups on day 14.

A dose response was observed with higher GMTs, GMFRs, and SCRs in the higher dose groups at the earlier time points (i.e. on day 14 and to a less extent on day 28) vs. later time points because antibody titres in the high dose groups (2×10^7 pfu and 1×10^8 pfu) tended to peak on day 28 and plateaued afterwards with a slight to moderate decrease from day 180 to day 360; instead in the lower dosing groups titres tended to continuously increase from day 28 to 180/360.

Though no correlate of protection is currently known for the V920 vaccine, and immunogenicity cannot directly be related to efficacy, the notably higher immune response at early time points favours the higher doses for a vaccine intended for emergency use in an outbreak situation. Between the doses 2×10^7 and 1×10^8 no notably difference in immune response could be observed (and confirmed in study V920-012). As long as a correlate of protection or a threshold is unknown, GMTs are considered a more robust value than seroconversion rates with an arbitrary threshold of 200 EU/ml. The phase I immunogenicity data do overall indicate an immune response sustainable through day 360.

Main studies

The immunogenicity of V920 was evaluated using validated assays in the V920-009, V920-011, and V920-012 trials. The immunogenicity endpoints included binding antibodies measured by GP-ELISA and neutralizing antibodies measured by PRNT at baseline, Day 28/Month 1, Day 180/Month 6, and Months 9 to 12/Month 12 post-vaccination. Immunogenicity was also assessed at Month 24 post-vaccination in the V920-012 trial.

For the V920-009, V920-011, and V920-012 trials, the immunogenicity analyses included assessment of the GMT, GMFR, and seroresponse in the GP-ELISA and the PRNT assays. In all phase 2 trials, for ELISA antibody titres, seroresponse was defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 2-fold increase in ZEBOV IgG compared with baseline (primary endpoint), or at least a 4-fold increase (secondary endpoint).

V920-009 (PREVAIL)

The V920-009 "PREVAIL" trial was originally designed as a Phase 2/3 randomized, double-blind, placebo-controlled safety and efficacy trial of 2 leading Ebola vaccine candidates (V920, provided by MSD, and ChAd3-EBO Z, provided by GlaxoSmithKline) in adults 18 years of age or older in Liberia. Due to low EVD incidence, the V920-009 protocol was amended to enlarge the immunogenicity portion of the sub-study and to cancel the Phase 3 efficacy portion of the trial. The initial target of recruiting 600 adults to the Phase 2 immunogenicity part of the trial was achieved in March 2015 and subsequently expanded to recruit a total of 1500 subjects with follow-up for 12 months in order to obtain more safety and immunogenicity data. Group A [n=500] received ChAd3-EBO Z, Group B [n=500] received V920, and Group C [n=500] placebo. Even though the efficacy part of the study was cancelled, the protocol was further amended to include a ring vaccination strategy following three new EVD cases observed in November 2015 near Monrovia (Liberia), and to extend safety and immunogenicity follow-up to 2 or 3 years post-vaccination. Ring vaccination data were collected and published (Gschell 2017, Bolay 2019), and reportedly do not add important safety information to the database. Since V920-009 is a supportive Phase 2 trial, the limited number of vaccinated subjects (n=444), the absence of identification of SAE through a passive follow-up and the obtention of immunogenicity data with a non-validated assay, these data are not considered critical for the safety, immunogenicity and efficacy assessment.

Study population and design

A total of 500 subjects were randomized and received V920. A majority of subjects were male (62.6%), and all subjects were Black or African. The median age was 29.0 years (range: 18 to 75 years). Twenty-two subjects (4.4%) who received V920 were HIV-positive based on HIV antibody testing at the vaccination visit. However, the serum taken for HIV testing at the vaccination visit was only tested after the vaccination was completed for the V920-009 trial. Therefore, no criteria for CD4 count or antiretroviral therapy could be applied for patients' selection. Additional data is expected from an ongoing trial in HIV-positive subjects (V920-015).

The trial design is acceptable, allowing to assess immunogenicity, safety and reactogenicity compared to saline placebo (0.9% NaCl). As there was no known licensed vaccine to prevent EVD, the placebo group was also acceptable.

Immunogenicity analysis population

The FAS population served as the primary population for the analysis of immunogenicity and included 477 subjects who had complete specimen sets available for immunogenicity testing in the validated GP-ELISA and PRNT through Month 12 post-vaccination. Some subjects were excluded from the analysis due to unevaluable serology sample or a missing assay result (for GP-ELISA, n=13 and for PRNT, n=49).

Immunogenicity analyses were not conducted for the PP population since only 1 protocol deviation was identified.

Immunogenicity results

The V920-009 report presented immunogenicity data for the vaccine group but not for the placebo group, as only the samples of the vaccine group were analysed with the validated assays, whereas the placebo samples were analysed earlier with the non-validated assays. The immunogenicity data of the placebo group were referenced through a publication (Kennedy et al. NEJM 2015). The number of subjects included in the placebo group decreased from 471 at Week 1, to 468 at Month 1, to 458 at Months 6 and 12.

Ninety-seven (20.9%) of 464 subjects tested had a baseline GP-ELISA ≥ 200 EU/ml. GP-ELISA GMTs for the V920 overall FAS population were higher than baseline at Month 1, Month 6, and Month 12, with a peak occurring at Month 1. GMTs constantly declined from 994.7 EU/mL [95% CI 915.0, 1,081.3] at Month 1 to 661.4 EU/mL [95% CI 613.2, 713.4] at Month 12. GMTs were higher at baseline for males (140.8 EU/mL [95% CI 127.2, 156.0]) compared with females (87.6 EU/mL [95% CI 75.1, 102.2]), but tended to be higher at all post vaccination time points for females (1,112.6 EU/mL [95% CI 964.9, 1,282.9], 871.3 EU/mL [95% CI 756.7, 1,003.3], 818.2 EU/mL [95% CI 710.3, 942.6]) compared with males (930.6 EU/mL [95% CI 839.8, 1,031.3], 631.7 EU/mL [95% CI 578.6, 689.5], 582.2 EU/mL [95% CI 535.5, 633.0]).

GP-ELISA titres increased in the overall FAS population from baseline by approximately 8-fold at Month 1 and remained elevated (>5-fold) through Month 12.

Table 5. Summary of GMT for the GP-ELISA from Protocols 009, 011 and 012 clinical trials

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]
Protocol 009 [§]	117.9 (464) [107.9, 128.7]	994.7 (475) [915.0, 1,081.3]	712.2 (477) [659.4, 769.3]	661.4 (475) [613.2, 713.4]
Protocol 011 [§]	92.7 (503) [85.3, 100.9]	964.3 (443) [878.7, 1,058.3]	751.8 (383) [690.6, 818.4]	760.8 (396) [697.6, 829.8]
Protocol 012				
Combined Consistency Lots Group	< 36.11 (696) [<36.11, <36.11]	1,262.0 (696) [1,168.9, 1,362.6]	1,113.4 (664) [1,029.5, 1,204.0]	1,078.4 (327) [960.6, 1,210.7]
High Dose Group	< 36.11 (219) [<36.11, <36.11]	1,291.9 (219) [1,126.9, 1,481.2]	1,189.5 (215) [1,036.7, 1,364.9]	1,135.5 (116) [934.8, 1,379.3]
Placebo Group	< 36.11 (124) [<36.11, <36.11]	< 36.11 (124) [<36.11, <36.11]	< 36.11 (123) [<36.11, <36.11]	< 36.11 (65) [<36.11, <36.11]
<p>The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009 and 011 and consists of all vaccinated subjects with serology data and had a serum sample collected within an acceptable day range.</p> <p>The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.</p> <p>n = Number of subjects contributing to the analysis.</p> <p>CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer</p> <p>*Protocol 011 from Month 9-12</p> <p>[§]Protocols 009 and 011 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers</p>				

93.8% of subjects had a seroresponse defined as a ≥ 2 -fold increase from baseline and 200 EU/mL at any time post vaccination for the GP-ELISA. 82.3% of subjects had a seroresponse defined as a ≥ 4 -fold increase from baseline at any time post vaccination. Overall, 90.0% [95% CI 86.9%, 92.6%] of subjects in the FAS population had seroconverted (defined as a ≥ 2 -fold increase from baseline and ≥ 200 EU/mL) at Month 1. The proportion only slightly decreased to 80.1% [95% CI 76.2%, 83.7%] at Month 12. Overall, 76.8% of subjects [95% CI 72.7%, 80.6%] had a seroresponse, defined as a ≥ 4 -fold increase from baseline for the GP-ELISA at Month 1. The proportion of subjects declined to 61.1% [95% CI 56.5%, 65.6%] at Month 12.

The trend for PRNT GMTs is comparable to what was observed for the ELISA GMTs. Like for the ELISA GMTs, also PRNT GMTs were higher than at baseline for all time points after vaccination and peaked in month 1. GMTs declined from 116.8 [95% CI 106.0, 128.8] at Month 1 to 76.8 [95% CI 69.9, 84.4] at Month 6 and raised again to 100.4 [95% CI 91.4, 110.3] at Month 12.

Table 6. Summary of GMT for the PRNT from Protocols 009, 011 and 012 clinical trials

Trial	Baseline GMT (n) [95% CI]	Month 1 GMT (n) [95% CI]	Month 6 GMT (n) [95% CI]	Month 12* GMT (n) [95% CI]
Protocol 009 [§]	< 35 (428) [<35, <35]	116.8 (477) [106.0, 128.8]	76.8 (477) [69.9, 84.4]	100.4 (476) [91.4, 110.3]
Protocol 011 [§]	< 35 (438) [<35, <35]	116.0 (437) [105.7, 127.4]	95.3 (382) [86.3, 105.3]	119.9 (396) [107.9, 133.2]
Protocol 012				
Combined Consistency Lots Group	< 35 (696) [<35, <35]	202.1 (696) [187.9, 217.4]	266.5 (664) [247.4, 287.0]	271.4 (327) [243.4, 302.7]
High Dose Group	< 35 (219) [<35, <35]	236.1 (219) [207.4, 268.8]	302.1 (215) [265.2, 344.1]	323.7 (116) [269.5, 388.8]
Placebo Group	< 35 (124) [<35, <35]	< 35 (123) [<35, <35]	< 35 (123) [<35, <35]	< 35 (65) [<35, <35]
<p>The Full Analysis Set population was the primary population for the immunogenicity analyses in Protocols 009 and 011 and consists of all vaccinated subjects with serology data and had a serum sample collected within an acceptable day range.</p> <p>The Per-Protocol Immunogenicity Population was the primary population for the immunogenicity analyses in Protocol 012 and includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.</p> <p>n = Number of subjects contributing to the analysis.</p> <p>CI = Confidence interval; GMT = Geometric mean titer; PRNT = Plaque Reduction Neutralization Test</p> <p>*Protocol 011 from Month 9-12</p> <p>[§]Protocols 009 and 011 used gamma irradiation of specimens to reduce risk of wild-type Ebola virus infection of laboratory workers</p>				

The immunogenicity data indicate an immune response at Month 1 sustainable through Month 12. The V920-009 trial is currently ongoing as a 5-year extension to evaluate immunogenicity at Months 24, 36, 48, and 60 post-vaccination. In addition, studies V920-015 and V920-016 will evaluate the boosterability of V920 after a second dose (2 months after dose 1). Since pregnancy was an exclusion criterion, few data are available in this vulnerable population.

V920-011 (STRIVE)

V920-011 was a Phase 2/3 randomized, open-label trial conducted in Sierra Leone to evaluate the safety and efficacy of V920 in a population of at-risk healthcare workers and Ebola front-line workers. However, like V920-009, V920-011 could not collect efficacy data due to the declining incidence of EVD at the time

of conduct. After the trial was launched at multiple vaccination clinics, an immunogenicity sub-study of approximately 500 participants was added to the protocol as amendment 3 (27 April 2015) and initiated. Immunogenicity analyses were performed pre vaccination and at Months 1, 6, and 9-12.

Study population and design

The study population included adults 18 years of age and older who were at high risk of exposure to Ebola infection through their work in the study districts. This included 1) personnel working in healthcare facilities where care was provided for Ebola patients; 2) personnel working in non-Ebola healthcare facilities who may have been exposed to undiagnosed Ebola-infected individuals; and 3) personnel working in one of the following front-line job categories: surveillance team, ambulance team, burial workers, or workers responsible for swabbing deceased persons. Subjects with HIV were excluded from the trial.

A total of 528 subjects were randomized. Of the 508 subjects who were vaccinated and provided samples for the assessment of immunogenicity, 506 subjects had at least one GP-ELISA result for immunogenicity samples collected within the allowed time windows and were included in the GP-ELISA FAS population. A total of 504 subjects had at least one PRNT result for immunogenicity samples collected within the allowed time windows and were included in the PRNT FAS Population. The ratio of male to female in vaccinated participants (58% versus 42%) was balanced. The mean age was 34.4 years of age. 100% of participants were black.

There was no separate randomization process for the subjects in the immunogenicity sub-study, which is acceptable.

The trial design included two vaccine arms (immediate or delayed) but no placebo arm. For the immunogenicity analysis, the data of both groups (immediate or delayed) were pooled, hence an assessment of immune responses against V920 compared to placebo cannot be made.

Immunogenicity analysis population

The (Full Analysis Set) FAS population served as the primary population for the analysis of immunogenicity and the PP population as the secondary. The FAS population included subjects who had at least one GP-ELISA result for immunogenicity samples collected within the allowed time windows. The Per Protocol (PP) population consisted of all randomized and vaccinated subjects with a serology assessment collected within the allowed time window. The PP population excluded subjects having baseline GP-ELISA assay results ≥ 200 EU/ml, violation of certain inclusion/exclusion criteria, and having a missing, unevaluable, or out-of-day-range serology result or sample at a particular time-point. A total of 424 subjects were included in the GP-ELISA PP population and 423 subjects were included in the PRNT PP population. The exclusion of subjects from the data analysis sets, for both the FAS and PP population as well as for the PRNT analysis was assessed and deemed acceptable.

Immunogenicity results

Seventy-six (15.0%) of the 506 subjects tested at baseline had a baseline GP-ELISA ≥ 200 EU/ml.

Values for GP-ELISA GMTs for the FAS population were higher than baseline (92.7 EU/mL 95% CI [85.3, 100.9]) at Month 1 (964.3 EU/mL [95% CI 878.7, 1,058.3]), Month 6 (751.8 EU/mL [95% CI 690.6, 818.4]), and Month 9-12 (760.8 EU/mL [95% CI 697.6, 829.8]) with a peak at Month 1 (table 5 above). GMTs plateaued thereafter from Month 6 through to Month 9-12.

Like in study V920-009, GP-ELISA GMTs in females were lower (76.8 EU/mL [95% CI 67.6, 87.2]) pre vaccination compared to males (106.3 EU/mL [95% CI 95.3, 118.6]), but higher at all time points post vaccination (1,057.9 EU/mL [95% CI 907.8, 1,232.7], 904.9 EU/mL [95% CI 787.1, 1,040.4], 972.9

EU/mL [95% CI 849.3, 1,114.4]) compared to males (903.4 EU/mL [95% CI 804.1, 1,015.0], 655.3 EU/mL [95% CI 591.2, 726.4], 631.2 EU/mL [95% CI 567.1, 702.5]).

Overall, GP-ELISA titres increased from baseline by approximately 11-fold at Month 1 and remained elevated (>8-fold) at subsequent time points.

Overall, 94.1% of subjects had a seroresponse defined as a ≥ 2 -fold increase from baseline and ≥ 200 EU/mL at any time post vaccination for the GP-ELISA. Overall, 90% (95 CI 86.8%, 92.7%) of subjects had this seroresponse at Month 1. The seroresponse rate only slightly decreased to 87.8% [84.1%, 90.9%] at Month 9-12.

A seroresponse defined as a ≥ 4 -fold increase from baseline was overall observed for 79.8% (95% CI 75.8%, 83.5%) of subjects at Month 1. The seroresponse rate only slightly decreased to 74.3% of subjects (95% CI 69.7%, 78.6%) through Month 9-12. A seroresponse defined as a ≥ 4 -fold increase from baseline at any time was observed in 87.3% (95% CI 84.0%, 90.2%) of subjects.

PRNT GMTs were almost comparable at Month 1 (116.0 [95% CI 105.7, 127.4]), Month 2 (95.3 [95% CI 86.3, 105.3]), and Month 9-12 (119.9 [95% CI 107.9, 133.2]) (see table 6 above). Overall, 81.5% of subjects had a seroresponse defined as a ≥ 4 -fold increase from baseline at any time post vaccination for the PRNT. Like for study V920-009 a positive correlation between GP-ELISA and PRNT results could be observed.

Gamma irradiation in studies V920-009 and V920-011

Gamma irradiation was performed for sera of V920-009 and V920-011 trial participants to eliminate the theoretical risk of Ebola infection for laboratory personnel processing specimens from at-risk populations.

Lower GMTs, GMFRs, and seroresponses have been observed in the V920-009 and V920-011 trials conducted in Sierra Leone and Liberia compared to the V920-012 trial conducted in the US, Spain and Canada. GMTs were 995, 712, and 661 in study V920-009 on Month 1, Month 6, and Month 12, and 964, 752, and 761, respectively for the same time points in study V920-011. GMTs in study V920-012 were higher at 1262, 1113, and 1078, respectively.

Whether this is due to the gamma irradiation or to the studied population is difficult to conclude. In addition, the potential clinical implication of this finding is unknown in lack of a correlate of protection.

Study V920-012

V920-012 was a Phase III randomized, double-blind, placebo-controlled study to evaluate the safety and immunogenicity of three consistency lots and a high dose lot of V920 compared to normal saline placebo in healthy eligible subjects between the ages of 18 and 65 years. The rationale for the study was to demonstrate lot consistency and obtain additional safety data. Subjects were randomized to 2:2:2:2:1 to receive a single 1mL intramuscular injection of $\geq 2 \times 10^7$ pfu lot A (n=266), $\geq 2 \times 10^7$ pfu lot B (n=265), $\geq 2 \times 10^7$ pfu lot C (n=267), $\geq 1 \times 10^8$ pfu "high dose lot" (n=266), or placebo (n=133).

The trial was conducted at 42 trial centres: 40 in the United States; 1 in Canada; and 1 in Spain. The immune response was assessed pre vaccination, at 28 days and 6 months post vaccination for all subjects. At the Month 6 post vaccination visit (the last visit in the base study), a target population of 600 subjects was asked to continue in a trial extension through Month 24 post vaccination to evaluate the durability of the V920 immune response. Additional blood samples were obtained at Months 12, 18, and 24 post-vaccination for the evaluation of immunogenicity by GP-ELISA and PRNT (PRNT60).

Study population

Healthy, eligible subjects between 18 and 65 years of age were randomised and vaccinated in the V920-012 trial. A total of 1197 subjects were randomized and 1194 (99.7%) subjects were vaccinated.

1138 (96.9%) subjects completed the Month 6 post vaccination visit. Of these, 566 (48.2%) subjects entered the trial extension through Month 24 post vaccination. During the trial extension 55 of the 566 subjects (9.7%) discontinued.

Overall, 1039 subjects were included in the PP immunogenicity population on Day 1.

Of the 1197 randomized subjects, 53.2% were female, 67.9% were White, and 85.2% were not Hispanic or Latino. The median age was 42.0 years (range: 18.0 to 65.0 years). The majority (94.7%) of subjects were enrolled in the US. The baseline characteristics for subjects who enrolled in the extension were generally consistent with those of the overall subject population in the base study. The majority of the subjects who entered the extension were female (55.1%), White (72.4%), and not Hispanic or Latino (85.9%). The median age was 42.0 years (range: 18 to 65 years).

Immunogenicity analysis population

The PP population served as the primary population for the analysis of immunogenicity data in this study. Subjects who were seropositive at baseline were excluded from the PP population. No analyses were performed on the FAS population because <10% of the subjects were seropositive at baseline.

Immunogenicity objectives

Two formal hypotheses were tested.

Primary immunogenicity objective:

1. To determine whether vaccination with V920 from 3 separate consistency lots results in equivalent immunogenicity.

Hypothesis: The GMT of anti-ZEBOV glycoprotein antibody measured by GP-ELISA at 28 days post vaccination will be equivalent across 3 consistency lots. The statistical success criterion for lot consistency requires the 2-sided 95% confidence interval on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio to be greater than 0.5-fold but no more than 2.0-fold.

Secondary immunogenicity objectives:

1. To estimate the anti-ZEBOV GP-ELISA GMTs measured at 28 days post vaccination in the 3 Consistency Lot groups (Lots A, B, and C combined) and the High Dose group.

No formal hypotheses were tested.

2. To estimate the GMTs of neutralizing antibodies measured by plaque reduction neutralization test (PRNT 60) at 28 days post vaccination in the 3 Consistency Lot groups (A, B, and C combined) and the High Dose group.

No formal hypotheses were tested.

3. To determine whether vaccination with V920 from 3 separate consistency lots results in equivalent immunogenicity.

Hypothesis: The geometric mean titre of anti-ZEBOV glycoprotein antibody measured by ELISA (GP-ELISA) at 28 days post vaccination will be equivalent across 3 consistency lots. The statistical success criterion for lot consistency requires the 2-sided 95% confidence interval on the pairwise lot-to-lot comparison of the GP-ELISA GMT ratio to be greater than 0.67- fold but no more than 1.50-fold.

Immunogenicity results

The primary and secondary objective to show lot-to-lot consistency between 3 manufacturing lots of V920 in respect to immunogenicity was met. Equivalence between the 3 manufacturing lots has been shown in

the primary and the secondary analysis. The lot-to-lot consistency in terms of immunogenicity between the 3 manufacturing lots of V920 at Day 28 post vaccination in the primary analysis was demonstrated for the PP cohort as the lower bound of the 95% CI of the GMT ratio between the groups being compared was greater than 0.5 and the upper bound was less than 2.0. Also, in all 3 pairwise comparisons in the secondary analysis lot-to-lot consistency could be shown, as the lower bound of the 95% CI of GMT ratio between the comparison lots was greater than 0.67 and the upper bound was less than 1.5 as requested.

Thirty-one (2.6%) of the 1197 subjects tested had a baseline GP ELISA ≥ 200 EU/ml.

GP-ELISA GMTs were comparable between the 3 manufacturing lots for all time points post vaccination, i.e. from Day 28 through month 24. GMTs for all 3 lots were highest at Day 28 and constantly declined through month 24. The decline was approximately 25% from day 28 to month 24. Values for the combined lots group were 1,262.0 [95% CI 1,168.9 to 1,362.6] on day 28 and 920.3 [95% CI 820.4 to 1,032.3] at Month 24. No meaningful difference between GP-ELISA GMTs of the 3 manufacturing lots group and the high dose group could be observed. The GMTs for the placebo group were less than the LLOQ of the GP-ELISA at all time points. Results of the GP-ELISA GMTs are provided in table 7 below and summarised in table 5 together with results from Protocols 009 and 011 (see Study V920-009).

Table 7. Summary of Geometric Mean Titres by Vaccination Group (Day 1 to Month 24) (GP-ELISA Per-Protocol Immunogenicity Population), V920-012

Assay Time Point	V920 Lot A (N=266) GMT (n) [95% CI]	V920 Lot B (N=264) GMT (n) [95% CI]	V920 Lot C (N=266) GMT (n) [95% CI]	V920 Combined Lots (N=796) GMT (n) [95% CI]	V920 High Dose (N=264) GMT (n) [95% CI]	Placebo (N=133) GMT (n) [95% CI]
GP-ELISA						
Day 1	< 36.11 (239) [<36.11, <36.11]	< 36.11 (231) [<36.11, <36.11]	< 36.11 (226) [<36.11, <36.11]	< 36.11 (696) [<36.11, <36.11]	< 36.11 (219) [<36.11, <36.11]	< 36.11 (124) [<36.11, <36.11]
Day 28	1,183.9 (239) [1,038.7, 1,349.4]	1,266.0 (231) [1,108.2, 1,446.2]	1,346.0 (226) [1,176.6, 1,539.9]	1,262.0 (696) [1,168.9, 1,362.6]	1,291.9 (219) [1,126.9, 1,481.2]	< 36.11 (124) [<36.11, <36.11]
Month 6	1,052.0 (226) [920.0, 1,203.0]	1,060.2 (221) [925.8, 1,214.2]	1,241.3 (217) [1,082.5, 1,423.4]	1,113.4 (664) [1,029.5, 1,204.0]	1,189.5 (215) [1,036.7, 1,364.9]	< 36.11 (123) [<36.11, <36.11]
Month 12	1,001.3 (107) [817.7, 1,226.1]	1,095.0 (117) [902.2, 1,329.0]	1,144.7 (103) [931.2, 1,407.1]	1,078.4 (327) [960.6, 1,210.7]	1,135.5 (116) [934.8, 1,379.3]	< 36.11 (65) [<36.11, <36.11]
Month 18	912.7 (105) [746.0, 1,116.6]	1,003.6 (109) [823.4, 1,223.2]	1,202.5 (100) [978.0, 1,478.6]	1,029.9 (314) [916.3, 1,157.5]	1,123.2 (111) [923.1, 1,366.5]	< 36.11 (65) [<36.11, <36.11]
Month 24	857.2 (102) [703.1, 1,045.1]	907.9 (105) [746.8, 1,103.7]	1,007.2 (96) [821.1, 1,235.5]	920.3 (303) [820.4, 1,032.3]	1,009.1 (105) [830.0, 1,226.7]	< 36.11 (65) [<36.11, <36.11]
<p>The per-protocol immunogenicity population includes all subjects who were compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.</p> <p>N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized.</p> <p>n = Number of subjects contributing to the analysis.</p> <p>< 36.11 were replaced with 36.11/2 in GMT calculations.</p> <p>CI = Confidence interval; GP-ELISA = Anti-Glycoprotein Human Enzyme-Linked Immunosorbent Assay (EU/mL); GMT = Geometric mean titer</p>						

GMFRs were comparable between the 3 manufacturing lots for all time points post vaccination. Titres for the V920 groups increased from baseline approximately 64-fold at Day 28 post vaccination and remained elevated approximately 48-fold from baseline at Month 24 post vaccination. No meaningful difference in GMFR between the combined manufacturing lots group and the high dose group could be observed. No GMFR was observed in the placebo group.

The proportions of subjects with a seroresponse defined as ≥ 2 -fold increase from baseline and ≥ 200 EU/mL at any time post vaccination ranged from 97.8% to 99.1% for the three V920 manufacturing lots groups and was 99.5% for the high dose group. The proportions of subjects with a seroresponse were generally comparable across the three V920 manufacturing lot groups across all time points post vaccination. No meaningful differences could be observed between the 3 manufacturing lots and the high dose group. Seroresponse rates are presented in table 8 below.

Table 8. Summary of Seroreponse Rates (≥ 2 -fold and ≥ 200 EU/mL) by Vaccination Group (Day 28 to Month 24) (GP-ELISA Per-Protocol Immunogenicity Population), study V920-012

Assay Time Point	V920 Lot A (N=266) Percent (m/n) [95% CI]	V920 Lot B (N=264) Percent (m/n) [95% CI]	V920 Lot C (N=266) Percent (m/n) [95% CI]	V920 Combined Lots (N=796) Percent (m/n) [95% CI]	V920 High Dose (N=264) Percent (m/n) [95% CI]	Placebo (N=133) Percent (m/n) [95% CI]
GP-ELISA						
At any time	98.7 (236/239) [96.4%, 99.7%]	99.1 (229/231) [96.9%, 99.9%]	97.8 (221/226) [94.9%, 99.3%]	98.6 (686/696) [97.4%, 99.3%]	99.5 (218/219) [97.5%, 100%]	4.0 (5/124) [1.3%, 9.2%]
Day 28	94.1 (225/239) [90.4%, 96.8%]	97.8 (226/231) [95.0%, 99.3%]	94.2 (213/226) [90.4%, 96.9%]	95.4 (664/696) [93.6%, 96.8%]	98.2 (215/219) [95.4%, 99.5%]	0.8 (1/124) [0.0%, 4.4%]
Month 6	95.1 (215/226) [91.5%, 97.5%]	95.0 (210/221) [91.3%, 97.5%]	95.4 (207/217) [91.7%, 97.8%]	95.2 (632/664) [93.3%, 96.7%]	96.3 (207/215) [92.8%, 98.4%]	0.8 (1/123) [0.0%, 4.4%]
Month 12	91.6 (98/107) [84.6%, 96.1%]	94.0 (110/117) [88.1%, 97.6%]	96.1 (99/103) [90.4%, 98.9%]	93.9 (307/327) [90.7%, 96.2%]	94.8 (110/116) [89.1%, 98.1%]	1.5 (1/65) [0.0%, 3.3%]
Month 18	91.4 (96/105) [84.4%, 96.0%]	94.5 (103/109) [88.4%, 98.0%]	92.0 (92/100) [84.8%, 96.5%]	92.7 (291/314) [89.2%, 95.3%]	95.5 (106/111) [89.8%, 98.5%]	3.1 (2/65) [0.4%, 10.7%]
Month 24	91.2 (93/102) [83.9%, 95.9%]	91.4 (96/105) [84.4%, 96.0%]	93.8 (90/96) [86.9%, 97.7%]	92.1 (279/303) [88.4%, 94.9%]	93.3 (98/105) [86.7%, 97.3%]	1.5 (1/65) [0.0%, 8.3%]

The per-protocol immunogenicity population includes all subjects who were generally compliant with the protocol, received vaccination, were seronegative at Day 1, and had a serum sample at one or more timepoints collected within an acceptable day range.
N = Number of subjects with serology data at one or more timepoints according to the treatment to which they were randomized.
m = Number of subjects seropositive.
n = Number of subjects contributing to the analysis.
Percent = m/n and represents proportion of subjects with GP-ELISA ≥ 2 -fold increase over baseline and ≥ 200 EU/mL.
At any time in sub-table % include all timepoints ≥ 28 d.

The proportions of subjects with a seroresponse defined as ≥ 4 -fold increase from baseline at any time post vaccination ranged from 98.7% to 99.2% for the three V920 manufacturing lots groups and was 99.5% in the high dose group. The proportions of subjects with a seroresponse were generally comparable across the three V920 manufacturing lot groups across all time points post vaccination. No meaningful differences could be observed between the 3 manufacturing lots and the high dose group.

PRNT GMTs for the three V920 lot groups were generally comparable. No meaningful difference between the 3 manufacturing lots groups and the high dose group could be observed. The PRNT GMTs tended to slightly increase from Day 28 to Month 12/18 (see table 6 under Study V920-009) and were slightly lower at month 24 (267.6 [95% CI 239.4, 299.2] for the combined lots; 342.5 [95% CI 283.4, 414.0] for the high dose group; < 35 [95% CI <35, <35] for the placebo group). This was the same for the final dose and the high dose groups. The PRNT GMT pattern did not notably differ from the ELISA GMT pattern.

2.4.4. Discussion on clinical pharmacology

The final nominal dose of 2×10^7 pfu was selected based on protection in NHP challenge model and clinical immunogenicity data that were collected within a phase 1 dose-finding program including 8 clinical trials. The clinical dose-finding program is considered comprehensive and the dose selection of a nominal dose of 2×10^7 is justified.

During the phase 1 clinical trials V920 has been administered across a broad spectrum of dose levels ranging from 3×10^3 pfu to 1×10^8 pfu to a total of 795 subjects. Immunogenicity was evaluated in Europe, US, Canada, and in non-epidemic African countries. The Phase 1 trials included 197 adult subjects who received a single dose of 2×10^7 pfu or higher of V920. Overall, 135 subjects received placebo in the Phase 1 blinded trials. Based on the commercial release potency range, the nominal doses of $\geq 2 \times 10^7$ pfu used in the clinical trials were representative of the commercial dose (i.e. $\geq 7.2 \times 10^7$ pfu). It has to be noted that the vaccine dose of $\geq 2 \times 10^7$ pfu, designated for clinical trials, was assigned using a non-validated potency assay. During development, a modified potency assay was designed and validated at a new laboratory. The clinical supplies were retested in this validated assay and resulted in a reassignment of the potency value to 7.2×10^7 pfu/dose.

To quantify total IgG binding antibodies against the rVSV Δ G-ZEBOV-GP, an indirect ELISA was used and the PsVNA or the PRNT assays to determine the virus neutralizing antibody levels. PsVNA was used in 7 out of the 8 Phase 1 studies but it was not possible to further validate it because of technical limitations. nAb were detected with this assay (as with the PRNT assay) but a difference between the PRNT and the

PsVNA with respect to nAb titres at the late time points was observed. PRNT assay was used in 1 out of the 8 studies (study V920-004). Both ELISA and PRNT assays were only validated for the phase 2/3 clinical development program.

The immunogenicity analyses in the clinical development program included GMTs, GMFRs, and seroconversion rates. Seroconversion was defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 4-fold increase in ZEBOV IgG compared with baseline in all phase 1 studies. In the phase 2/3 trials seroresponse defined as a post-vaccination ELISA titre ≥ 200 EU/mL that was also at least a 2-fold increase has been additionally evaluated (primary endpoint). Some subjects included in various Phase 1 studies were classified as seropositive at baseline. Baseline seropositivity could be due to previous EBOV exposure but might also be misclassified due to cross-reactivity to other viruses or to the performance of the technique. Gamma-irradiation may also interfere.

The applicant appropriately clarified the choice of the 200 EU/mL cut-off and the use of a dual criterion to determine a seroresponse. It cannot be excluded that the detection of ZEBOV GP-Ab at baseline in a certain proportion of samples could be due to cross-reactivity, however the definition of the seroresponse helps to minimize false-positive results. This is supported by the fact that the proportion of subjects seropositive at baseline in the V920-012 study was comparable to the proportion found in the V920-004 study conducted in the US and represent a minority of the study population ($n=31/1197$, 2.6%). Similarly, undetectable previous infection (no circulating EBOV-GP Ab) or interference with other antigens might cause false-negative results. CMV antigen has been shown to inhibit detection of EBOV-GP specific Ab. It is not known if this inhibitory capacity is restricted to CMV antigen or if other antigen non-related to EBOV may interfere with the performance of the test.

In the absence of Ab determination before vaccination or adequate identification of previously infected subjects at baseline, the role of any pre-existing immunity in the protection against EBOV infection cannot be strictly determined. Both the integrated summary of immunogenicity and correlates of protection reports may help to better understand the relevance of the immunogenicity data to predict protection and will be submitted post-authorisation.

The results of the phase 1 trials allowed to assess the anti GP antibody kinetics after vaccination. GMTs, GMFRs, and seroconversion rates were higher at all time points after Day 14 in the vaccine groups compared with the placebo groups, where overall no immune response was observed. No immune response was observed for any dose of EBOV-naïve group on Day 7. The immunogenicity of V920 was not evaluated at Day 7 in a population with pre-existing EBOV-specific Ab.

Antibody titres were measurable to a different extent in all dosing groups on Day 14. A dose response was observed with higher GMTs, GMFRs, and seroconversion rates in the higher dose groups, at the earlier time points (i.e. on Day 14, and less evident on Day 28). The difference in GMTs and seroconversion between lower and higher dose groups was smaller at later time points since antibody titres tended to continuously increase from Day 28 to 180/360 in the lower dosing groups whereas titres in the high dose groups (2×10^7 pfu and 1×10^8 pfu) tended to peak earlier (on Day 28) and plateaued afterwards with slight to moderate decrease from Day 180 to Day 360. Between the doses 2×10^7 and 1×10^8 no notably difference in immune response could be observed. This was confirmed in the Phase 3 trial V920-012.

The results from the phase 1 trials were confirmed in the 3 phase 2/3 trials conducted during the time of the 2014 to 2016 Ebola outbreak in at-risk populations in Liberia (V920-009) and Sierra Leone (V920-011), as well as a population not at risk (V920-012) in US, Canada and Spain. V920 elicited a sustainable immune response through Month 24 which was the longest follow up time in the phase 2/3 clinical development program during licensure (V920-012). Antibody peaked on Day 28 and more or less plateaued through Month 24 with only moderate decrease.

Immunogenicity was evaluated in Europe, Canada, and the US, as well as in African countries at risk or not at risk for Ebola. Lower GMTs, GMFRs, and seroresponse rates have been observed in the V920-009 and V920-011 trials conducted in Liberia and Sierra Leone compared to those observed in the V920-012 study conducted in the US, Canada and Spain. GMTs were 995, 712, 661 in V920-009 study on Month 1, Month 6, and Month 12, and 964, 752, and 761, respectively in study V920-011. GMTs in study V920-012 were 1262, 1113, and 1078, respectively for the same time points. Whether this is due to the gamma irradiation or to the population is difficult to conclude. In addition, the clinical relevance is unclear since a correlate of protection is not defined. Lot-to-lot consistency between three manufacturing lots containing the nominal final dose of 2×10^7 pfu was demonstrated in study V920-012.

The trend for PRNT GMTs is overall comparable to what was observed for the ELISA GMTs. PRNT GMTs peaked at Day 28 (V920-009 and V920-011 studies) or at Month 18 (V920-012 study) and plateau afterwards through Month 12 (V920-009 and V920-011 studies) or Month 24 (V920-012 study).

In study V920-009 and study V920-011 a higher immune response was observed in females compared with males. A sex-based difference in immune response is known from literature. Higher immune responses (ELISA GMTs) was also observed in subjects with pre-existing immunity, and in HIV-negative individuals compared with HIV-positive subjects. These findings are also known from other vaccines. The nAb titres (PRNT) were similar, regardless of pre-existing immunity. The clinical relevance of these findings with regard to clinical protection is currently unknown.

Immunogenicity was evaluated in 40 younger individuals 6 to 17 years of age. These limited data do not indicate a diminished immunogenicity in the paediatric population of that age.

A correlate of protection/protective titre associated with V920 is currently not known. In the efficacy ring trial V920-010 no immunogenicity was evaluated to directly estimate a protecting threshold on individual level. More data may become available post-authorisation.

The antibody kinetic in the phase 1 and phase 2/3 trials suggests a sustainable immune response with slight to moderate but continuous decline of antibodies through 6 to 24 months. This is more evident in the ELISA results than in the PRNT results. Long-term efficacy and immunogenicity of V920 are unknown. Without a correlate of protection or knowledge about a protective titre for V920, sustained long-term efficacy cannot be directly inferred from persisting antibody titres by ELISA for the time being.

The need (and optimal time point) for a booster dose are unknown. The V920-009 trial is currently ongoing in a 5-year extension to evaluate immunogenicity at Months 24, 36, 48, and 60 post-vaccination.

Pre-existing immunity to the VSV vector was explored in two Phase 1 studies. Based on the limited available data, there is currently no indication that pre-existing immunity to VSV would impact V920-induced immunogenicity. In addition, given that VSV is not endemic or epidemic in the EU or Africa, it is not anticipated that there will be significant pre-existing anti-VSV immunity present in the areas most at risk of future Ebola outbreaks.

Finally, adaptive (B- and T-cell) and innate responses were to be explored using various techniques such as EliSpot, flow cytometry or mass spectrometry. Results of the exploratory assays will be reviewed and submitted together with the related publications post-approval.

2.4.5. Conclusions on clinical pharmacology

Protective immunity against Ebola virus infection and disease is not well understood. It seems to be mediated by both humoral and cellular immune responses (both innate and adaptive immunity). The quantity but also the quality of Ab (isotype, subclass, epitopes, functionality, etc) are thought to be important for protection and may depend on the cellular immune responses.

Currently, there is no identified immune correlate of protection able to predict efficacy in humans and no immune correlate derived from bridging animal challenge data to humans.

The aggregated immunogenicity data in human, i.e. results of both GP-specific Ab and ZEBOV-neutralizing Ab, support the finally selected dose of $\geq 2 \times 10^7$ pfu. The data indicate a robust and sustainable immune response induced by V920 at a dose level of $\geq 2 \times 10^7$ pfu. GP-specific antibody titres were measurable on Day 14 and peaked on Day 28. A slight to moderate decline of antibodies through 12 to 24 months of follow up, in healthy adults from EU, US, Canada and African countries was observed thereafter. Like for the ELISA GMTs, PRNT GMTs were measurable from Day 14 through Month 12 to 24. The duration of immunogenicity after two years and the need for a booster are currently not known.

Without a correlate of protection or knowledge about a protective titre for V920, (sustained) efficacy cannot certainly be inferred from the (persisting) antibody titres. The search for statistical correlates of protection that is ongoing might help to demonstrate the clinical relevance of the immune responses. This emphasizes the critical need of effectiveness data to further confirm or document the protective effect of this vaccine.

Lot-to lot consistency in terms of immunogenicity was demonstrated.

Recommendations for future clinical pharmacology development

- The Integrated Summary of Immunogenicity results should be submitted as soon as available.
- The Immunobridging analysis and the Predictive Threshold of Protection analysis (Correlate of Protection) data should be submitted as soon as available.
- The final report on immunogenicity assessment based on baseline antibody status should be submitted as soon as available.
- The long-term follow-up data from study V920-009 (PREVAIL) should be submitted as soon as available.
- Exploratory data for the Phase 1 studies and the related publications should be submitted as soon as available.

2.5. Clinical efficacy

2.5.1. Main study

V920-010; the Guinea ring vaccination, open-label, cluster-randomized trial; Ebola Ça Suffit!

V920-010 was a field-based, open-label, cluster-randomized, controlled trial designed to evaluate the efficacy, effectiveness, and safety of a single administration of V920 at a nominal dose of the 2×10^7 pfu in the prevention of EVD when implemented as ring vaccination during an outbreak. This section covers Part A of the study, i.e. the ring vaccination trial.

The trial was sponsored and implemented by the WHO.

Methods

Study Participants

The trial was based in Guinea, during the 2014–2016 outbreak of Ebola virus disease in West Africa. This area was chosen as EVD cases were confirmed in this country at the time of trial start.

In this ring vaccination trial, a person newly diagnosed with EVD was assigned the index case, around whom an epidemiologically defined ring was formed. A cluster (ring) consisted of a list of contacts and contacts of contacts (CCCs) of the index case, regardless of their eligibility for V920 vaccination in the trial. From the complete cluster list, preliminary inclusion/exclusion criteria were applied to generate a list of all potential eligible CCCs to be approached for consent.

Eligible CCCs were all ring participants aged ≥ 18 years, who did not have either of:

- history of EVD
- anaphylaxis to vaccine component
- severe illness
- history of clinically important immunodeficiency
- pregnancy or breast-feeding, or
- receipt of other investigational products in the previous 28 days

After protocol Amendment V0.4 (dated 08-JUL-2015), the age limit was lowered down to 6-17 years.

Treatments

Subjects were assigned to either immediate vaccination or delayed vaccination (see also the following sections). At the Day 0 Visit, inclusion/exclusion criteria were checked, and after obtaining informed consent, eligible subjects assigned to immediate vaccination were given a single IM dose of 2×10^7 pfu V920 at the initial study visit (i.e. Day 0 from randomization), while those assigned to delayed vaccination received V920 vaccine 21 days after randomization (i.e. Day 21).

Objectives

This trial was designed to evaluate the efficacy, effectiveness, and safety of V920 in the prevention of EVD when implemented as ring vaccination during an outbreak.

Primary Objective:

To evaluate the efficacy of the vaccination against laboratory-confirmed Ebola virus diseases (EVD) by conducting a clinical trial that compares the immediate and delayed ring vaccination.

Secondary Objectives:

- a) To assess the overall effectiveness of the vaccine (cumulative incidence) in the prevention of laboratory-confirmed EVD within the ring after 84 days of follow-up.
- b) To assess the efficacy of the vaccine against death by laboratory-confirmed EVD.
- c) To assess the efficacy of the vaccine against probable and suspected EVDs.
- d) To evaluate the safety of the vaccine by assessing the SAEs for 84 days.

Outcomes/endpoints

The primary efficacy endpoint was confirmed EVD, defined as:

- any probable or suspected case from whom a blood sample taken was laboratory confirmed as positive for EVD; or
- any deceased individual with probable EVD, from whom a post-mortem sample taken within 48 hours after death was laboratory confirmed as positive for EVD

Laboratory confirmation is obtained by real-time (RT) validated reverse transcription PCR test for Ebola viral nucleic acid. Confirmed cases were thus defined per WHO guidelines as any suspected or probable case with a positive laboratory result.

The secondary efficacy endpoints were probable EVD and suspected EVD, and safety outcomes.

Probable EVD: Any suspected case evaluated by a clinician OR any person who died from "suspected EVD" and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease.

Suspected EVD: Any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a suspected, probable or confirmed Ebola case (EVD), or a dead or sick animal OR any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia/loss of appetite, diarrhoea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccups; OR any person with unexplained bleeding OR any sudden, unexplained death.

Ring participants were followed for EVD until the outbreak ended. The mechanisms put in place to monitor EVD and safety included:

- The national Ministry of Health (MoH) surveillance team, which was independent of the trial teams and conducted follow-up of the contacts for the first 21 days following the confirmation of the index cases (contact tracing);
- The study team, which performed follow-up of the contacts-of-contacts via study visits on Days 3, 14, 21, 42, 63 and 84 post-vaccination scheduled for AEs and SAEs;
- The community ring representatives, which reported EVD cases via phone calls;
- New cases of EVD admitted to the Ebola Treatment Centres (ETC) were reported by the MoH/WHO centre. EVD cases were confirmed by PCR.

Sample size

Pre-specified sample size calculations assumed that each cluster would contain an average of 50 consenting participants. 90% power was required to reject the null hypothesis of no vaccine efficacy, with the probability of a type I error (i.e. α level) set at 5%, for a two-sided test of significance.

To account for the clustering (i.e. the design effect), an intra-class correlation coefficient of 0.05 was assumed.

Sample sizes were calculated by varying the percentage of contacts becoming infected and developing Ebola virus disease (i.e. the illness rate) between 1% and 5%. The potential vaccine efficacy was also varied from 50% to 90%. For example, if the vaccine efficacy was 70% and the infection rate 2%, then a total of 190 clusters would be needed (95 in each arm). However, if the vaccine efficacy was 90%, with a 2% infection rate, then a total of 98 clusters would be needed (49 in each arm).

The trial was done in an adaptive manner, for which a two-sided symmetric O'Brien-Fleming alpha spending strategy truncated at an absolute value of 3.00 was used (the O'Brien-Fleming threshold for the interim analysis was 0.0027).

This trial was designed in an adaptive fashion with the most likely target being about 100 randomized rings to either immediate or delayed vaccination at the interim analysis and 190 rings at the final analysis. No boundary for futility or low conditional power was pre-specified, although the trial could have been expanded in an adaptive fashion if the observed event rate was lower than expected. The data and safety monitoring board could decide whether to continue or stop the trial, according to success, failure, or insufficient evidence.

Thus, the exact timing of the interim analyses was not pre-planned and depended on various factors, including, but not limited to, the total number of EVD events observed in the trial. In particular, the timing could have been modified if the observed EVD rate was higher or lower than the assumed value of 2% during the trial period.

Randomisation

Randomization was at the level of cluster, not at the individual level. Randomization took place only when the numeration of CCCs for a ring was closed. The ring randomization was in a 1:1 ratio to either immediate vaccination or delayed vaccination with a single dose of V920.

Eligible subjects cluster-randomized to immediate vaccination had only one opportunity to give their informed consent (Day 0), while eligible subjects assigned to the delayed clusters had 2 opportunities to consent, on Day 0 and on Day 21.

Due to the identified consenting issues in 363 individuals (documented in monitoring reports), a re-consenting effort was implemented by the trained trial team for all individuals in rings 1 to 90 who had not yet completed their last visit as a means to ensure that the consent was documented appropriately.

The rate of subjects consenting on Day 0 is around 20% higher in the immediate vaccination arm ($2151/3232 = 66.6\%$) than in the delayed vaccination arm ($1435/3096 = 46.4\%$). This might suggest that randomization results were known to a large extent prior to consenting. The impact of this potential selection bias is not known.

Blinding (masking)

The study was open label, so blinding of participants and investigators/field teams was not possible.

The vaccine vials had the manufacturer's labelling and were not designed for a specific subject.

The Guinea national Ebola surveillance team and the trial team were independent of each other; the trial team did not communicate any specific information regarding any of the listed contacts and contacts of contacts to the surveillance teams and associated laboratories. For example, it did not provide information with regards to which EVD index cases were used to form a new ring or which people would be included in a given cluster or ring. Surveillance laboratory staff was therefore blinded to the randomization to the immediate or delayed vaccination or vaccination status of any suspected case sample being tested.

Information about the allocation to immediate or delayed vaccination was made available for a given ring only after the enumeration of the ring members was completed and registering the ring with the DMC at CTU Bern. To conceal randomization until all informed consents had been obtained for a given ring, the file(s) containing information about allocation were not opened by any person involved in recruiting participants and other trial personnel (including the statistician responsible for the data analysis) until the

primary analysis was completed. If such file(s) were opened, a signed and dated note-to-file was stored in the respective subfolder of the CTU Bern trial file indicating the name of the person who opened it, responsible person who authorized the opening, and reason for the opening.

Statistical methods

The incidence of EVD was compared between the 2 arms over defined time periods measured from the time of randomization of each ring. Vaccine efficacy and effectiveness were estimated as the overall reduction in the EVD incidence in rings that were randomized to immediate vaccination compared to those randomized to delayed vaccination. VE was defined as 1- the hazard ratio for EVD (i.e., the estimated hazard of EVD for individuals in a ring that receives immediate vaccination over the estimated hazard of EVD for individuals in a ring that receives delayed vaccination).

The operational definition of per protocol analysis period censored events of EVD occurring <D days after vaccination (immediate arm) or after enrolment (delayed arm). In practice, D was later set at 10 days. Thus, by default, only confirmed EVD cases occurring ≥10 days post-randomization were valid endpoints for the trial to account for the incubation and vaccine response periods.

In the delayed vaccination arm, participants were administratively censored 10 days after vaccination. Participants in the immediate vaccination arm were administratively censored on the same date as the last participant censored in the delayed vaccination arm or at 84 days (end of follow-up period), whichever comes first. Any individual who is lost to follow-up was censored at the last known date of observation.

Vaccine efficacy or vaccine effectiveness against EVD was assessed across 9 different populations (see table 9 below). Many of these analyses were suggested in published commentary or based on feedback from regulatory agencies. In addition, 8 out of these 9 populations described in table 9 (except population #2) were used to assess vaccine efficacy against the EVD death endpoint.

The primary analysis (not pre-specified) compared subjects vaccinated at Day 0 in the immediate arm vs. subjects who consented on Day 0 in the delayed arm for the estimation of vaccine efficacy.

Table 9. V920-010: Study populations for primary and secondary analyses

Vaccine Efficacy against EVD	
1	Randomized rings: All vaccinated in immediate (A) versus all eligible and consented on Day 0 visit in delayed (B)
Vaccine Effectiveness against EVD	
2 ^a	Randomized rings: All vaccinated in immediate (A) versus all eligible and consented in delayed (B)
3	Randomized rings: All vaccinated in immediate (A) versus all eligible in delayed (B)
4	Randomized rings: All eligible in immediate (A) versus all eligible delayed (B)
5	Randomized rings: All CCCs in immediate (A) versus all CCCs in delayed (B)
6	All rings: All immediately vaccinated (A) versus all CCCs in delayed clusters plus all never vaccinated in immediate or non-randomized (B)
7	All rings: All vaccinated in immediate (A) versus all eligible in delayed plus all eligible never vaccinated in immediate (B)
8	All rings: All CCCs in immediate (A) versus delayed (B)
9	All rings: All vaccinated in immediate (A) versus all eligible never vaccinated in immediate (B)
^a Note: Not presented in the V920-010 CSR	

Of note, the primary analysis in published literatures compared all vaccinated in immediate arm versus all eligible subjects assigned to delayed vaccination arm (Population #3). Based on relative clarity regarding

timing of consent on Day 0, subjects labelled in the database as consented at Day 0 were proposed to be utilized as the final primary efficacy analysis population in this submitted CSR (Population #1).

Vaccine effectiveness calculations were based on an estimation of the overall reduction in EVD in rings including vaccinated and non-vaccinated subjects. The estimation of transmission parameters was not completed at the time of the evaluation procedure.

Finally, the applicant included an analysis to compare the incidence of EVD with onset before the 10-day post-vaccination cut-off in the immediate versus the delayed vaccination clusters. This analysis served to respond to a regulatory agency comment on interim results of the trial.

DSMB recommendation

An independent DSMB was incorporated in the protocol to review efficacy and safety data on a monthly basis. On 3 July 2015, an interim analysis was performed based on 48 clusters in the immediate arm and 42 clusters in the delayed arm. The primary analysis compared all vaccinated individuals from the immediate arm with all eligible individuals in the delayed arm. At 10 days or more post-randomisation, no cases of confirmed EVD occurred in the immediate arm compared with 16 cases (from 7 rings) in the delayed arm. Results showed 100% efficacy, but p-value did not cross the interim stopping threshold of 0.0027 for efficacy (p-value 0.0036 according to Fisher's exact test comparing the proportions of clusters with one or more eligible case).

Due to the low likelihood of being able to recruit substantial numbers of additional rings, the DSMB decided to stop randomization and to immediately vaccinate all eligible subjects in any newly identified rings. In addition, the trial was extended to areas of Sierra Leone adjoining the border of Guinea and was amended to include children 6 to 17 years of age.

Results

Subject disposition and baseline demographic characteristics

A total of 476 confirmed EVD cases were identified. Of these, 361 cases were excluded and rings were not defined around them. The majority (76%) of excluded cases were due to distance, delayed reporting, or inadequate study team capacity. Therefore, rings were defined for the remaining 115 cases in Guinea and for 2 additional cases from Sierra-Leone, resulting in a total of 117 rings comprising a total of 11,841 CCCs.

Among 11,841 subjects enrolled into the trial, 9,096 subjects were from 98 randomized clusters, comprising of 4,539 CCCs (51 clusters) in immediate vaccination arm and 4,557 CCCs (47 clusters) in delayed vaccination arm.

Of 19 non-randomized clusters (2,745 CCCs), 3 rings were constituted before randomization was initiated (i.e. pilot phase of trial) and 16 constituted after randomization discontinuation as per the DSMB recommendation. Only immediate vaccination was available for subjects in the non-randomized clusters.

The proportion of CCCs eligible for vaccination with V920 was 71% (3,232/4,539) in the immediate arm and 68% (3,096/4,557) in the delayed arm. The proportion of CCCs who were eligible and provided consent is lower for the subjects randomized to immediate (47%) vs. delayed vaccination arms (56%) (respectively 2151 and 2539 including 1435 consenting on Day 0). Overall, the vaccination rate was 66% (2,119/3,232) in the immediate arm and 66% (2,041/3,096) among the eligible subjects of the delayed arm who gave consent either on Day 0 or Day 21.

The median age for 117 index cases was 35 years in both the immediate and delayed randomized rings and 23 years in the non-randomized rings. Overall, females comprised 59.8% of the index cases.

Approximately 77% of the clusters in the randomized arms were located in rural areas, compared to 47% of clusters in the non-randomized group (Table 10).

Table 10. V910-010 – Baseline Characteristics of Index Cases and Clusters

	Randomized		Not Randomized	All Clusters (117 clusters)
	Allocated to Immediate Vaccination (51 Clusters)	Allocated to Delayed Vaccination (47 Clusters)	Allocated to Immediate Vaccination (19 Clusters)	
Index cases used to define clusters¹				
Age in years	35 (18 - 43)	35 (27 - 50)	23 (13 - 42)	35 (20 - 47)
Females	27/51 (52.9%)	31/47 (66%)	12/19 (63.2%)	70/117 (59.8%)
Dead at time of randomization (95% CI)	30/51(58.8%) (0.44 to 0.72)	32/47(68.1%) (0.53 to 0.81)	9/19 (47.4%) (0.24 to 0.71)	71/117(60.7%) (0.52 to 0.69)
Time from symptom onset to hospitalisation/isolation of case, days	3.9 (2.9)	3.8 (2.6)	3.2 (2.4)	3.7 (2.7)
Time from symptom onset of case to randomization of cluster, days	9.7 (5.3)	11 (4.1)	-	10.3 (4.8)
Time from symptom onset of case to inclusion of cluster, days	9.8 (5.1)	10.9 (4.1)	7.3 (3.7)	9.9 (4.6)
Cluster characteristics				
Clusters located in rural areas	39/51 (76.5%)	36/47 (76.6%)	9/19 (47.4%)	84/117 (71.8%)
Median number of people in cluster ¹	80 (64 - 101)	81 (69 - 118)	105 (49 - 185)	83 (66 - 115)

¹ Data are presented as median (25th quantile - 75th quantile), n/N (%), or mean standard deviation (SD).

The index cases and clusters randomly allocated to immediate vaccination vs. delayed vaccination were generally comparable at baseline, including age of index cases, the time from symptom onset to hospitalization/isolation of index cases or inclusion of clusters, and location of clusters (Table 10).

The proportion of index cases that were dead at the time of randomization was slightly higher in the delayed arm compared to the immediate arm, which did not appear to result in more high-risk contacts in delayed arm (Table 11 below). The average cluster size in delayed vaccination arm was 30.5 compared to 42.2 in immediate vaccination arm, when the primary analysis is restricted to eligible subjects who consented on Day 0 only.

The majority of eligible CCCs were male, with females comprising 30% to 37% of consented subjects in the randomized rings and 35% in the non-randomized group (Table 11 below). The mean age of consenting CCCs was 35 years. There were 536 eligible, consented subjects ≥65 years of age, and 194 children and adolescents 6 to 17 years of age were enrolled in nonrandomized group and vaccinated (Table 11 below).

The baseline characteristics of the eligible CCCs with consenting status in the immediate versus the delayed arms are presented in Table 11 below. The two arms are largely comparable.

Notably, more than 80% of consenting CCCs were the contacts of contacts of the index cases (Table 11). The proportion of contacts classified as high-risk was slightly higher in the immediate vaccination arm (15%), compared with subjects in the delayed vaccination arm who consented on Day 0 (12%) and subjects who consented on Day 21 (5%).

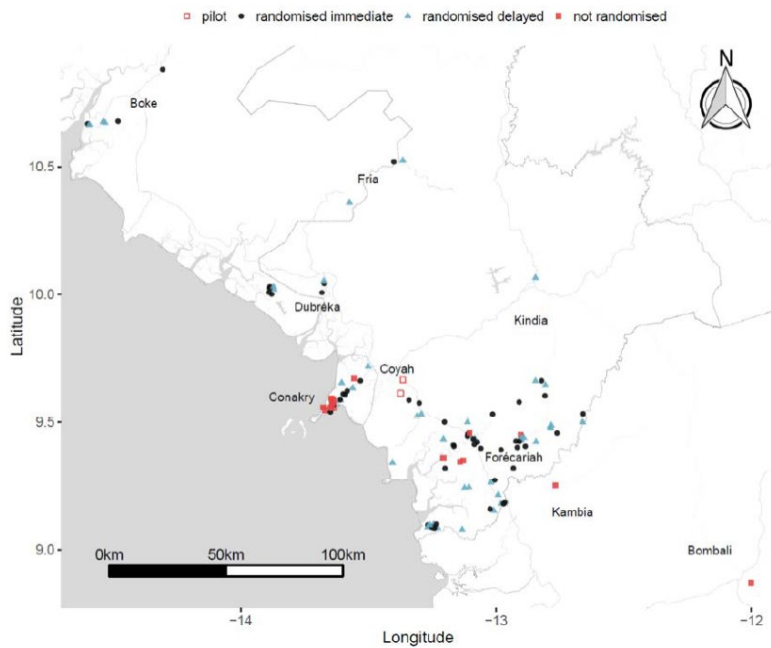
Table 11. Baseline Demographic Characteristics of Subjects and Contacts with Index Case

Eligible (adults ≥ 18 years of age, non-pregnant, non-breastfeeding*)									
	Randomized					Not randomized**		All	
	Assigned to immediate vaccination (51 clusters, n=3232)		Assigned to delayed vaccination (47 clusters, n=3096)			Assigned to immediate vaccination (19 clusters, n=2006)		All clusters (117 clusters, n=8334)	
	Consented	Not consented	Consented on visit day 0†	Consented on visit day 21†	Not consented	Consented	Not consented	Immediately vaccinated	Delayed or never vaccinated
Subject characteristics									
Number of subjects	2151	1081	1435	1104	557	1678	328	3796	4538
Age (years)	40 (29–55)	30 (25–45)	39 (27–53)	37 (27–50)	32 (23–45)	30 (22–44)	25 (18–35)	35 (25–50)	35 (25–50)
Age Group									
6 - 17	0	0	0	0	0	194 (11.6%)	78 (23.8%)	194 (5.1%)	78 (1.7%)
18 - 39	1032 (48%)	728 (67.3%)	728 (50.7%)	586 (53.1%)	357 (64.1%)	947 (5.1%)	171 (52.1%)	1958 (51.6%)	2591 (57.1)
40 – 64	889 (41.3%)	277 (25.6%)	573 (39.9%)	427 (38.7%)	168 (30.2%)	456 (27.2%)	64 (19.5%)	1336 (35.2%)	1518 (33.5%)
≥ 65 years	230 (10.7%)	76 (7.0%)	134 (9.3%)	91 (8.2%)	32 (5.7%)	81 (4.8%)	15 (4.6%)	308 (8.1%)	351 (7.7%)
Females	640/2151 (30%)	608/1081 (56%)	428/1434 (30%)	404/1104 (37%)	319/557 (57.3%)	593/1678 (35%)	179/328 (54.6%)	1223/3796 (32%)	1948/4537 (43%)
Contacts with index cases									
No detailed contact information (no consent)	0/2151 (0%)	1081/1081 (100%)	0/1435(0%)	0/1104(0%)	557/557 (100%)	0/1678(0%)	328/328 (100%)	0/3796	1966/4538 (43%)
Contact of contact‡	1727/2151 (80%)	--	1160/1435 (81%)	971/1104 (88%)	--	1418/1678 (85%)	--	3116/3796 (82%)	2160/2572 (84%)
Contact‡	424/2151 (20%)	--	275/1435 (19%)	133/1104 (12%)	--	260/1678 (15%)	--	680/3796 (18%)	412/2572 (16%)
High-risk contact‡	330/2151 (15%)	--	171/1435 (12%)	58/1104 (5%)	--	246/1678 (15%)	--	574/3796 (15%)	231/2572 (9%)
NOTE: Age Group details were added. n=number eligible subjects in each arm Data are median (25th quantile - 75th quantile) or n/N (%). * Eligible subjects in randomized and non-randomized rings are included in this table. ** Six non-randomized rings included children aged 6 years and older (n=273). † Informed consent was obtained either during the first visit (day 0) or second visit (day 21) of trial team. ‡Proportion calculated among individuals with available contact information. Two individuals were pregnant and one was severely ill.									

Recruitment

The trial was conducted in the region of Basse-Guinée, a coastal area of Guinea, West Africa, and comprised the capital Conakry and surrounding prefectures in Guinea (Figure 1). There were 9 prefectures in Guinea represented in the trial. This area was chosen because it was the only area of Guinea in which cases of EVD were confirmed at the time of the start of the study. As the epidemic was still active in Sierra Leone, it was proposed to extend the Ring vaccination to two prefectures in Sierra Leone adjoining the borders of Guinea (Kambia and Bombali) as per protocol V0.5.

Figure 2. Study Area of the Ring Vaccination Trial



Recruitment in the pilot phase occurred from March 23 to April 1, 2015. The randomization occurred over 17 weeks, from April 1 to July 21, 2015. After July 27, all consenting subjects received the vaccine immediately. The last subject was enrolled in November 2015. Last subject last visit (LSLV) was on 20 January 2016. The study lasted (from first enrolled subject to Day 84 visit of the last subject followed) 303 days (~10 months).

Conduct of the study

World Health Organization (WHO) was the study sponsor and MSD/NewLink is the V920 vaccine manufacturer.

The trial's steering committee coordinated the project. The Guinean health authorities, WHO, and MSF were part of the trial's Steering Committee, presided over by National Institute of Public Health (INSP), Norway.

MSF led the trial operations within the country, in close collaboration with Guinean authorities, the WHO as well as other partners on the field. Guinean health authorities contributed to the implementation of this trial, most specifically by providing medical advice, communication methods, and ownership of federal land.

WHO oversaw data management, statistical analysis and activity modelling. Moreover, WHO coordinated all GCP training and monitoring operations, the Data Safety Monitoring Board, as well as the independent trial audit. WHO provided assistance during implementation of the trial on the field, where necessary.

The University of Bern, the London School of Hygiene and Tropical Medicine (LSHTM), the University of Florida and Public Health England contributed to the development of the protocol, prepared the statistical analysis plan, contributed to epidemiological methods and analysis, provided trial expertise ensured data management, ensured statistical analysis of trial results, and mathematical modelling.

The Centre for Vaccine Development Mali and University of Maryland provided the trial team with GCP training and ensured clinical trial control.

The trial team headquarters was located at a single centre in the region of Basse-Guinée (Guinea) in Conakry from which this trial was conducted under the responsibility of the PIs. The trial's field teams travelled from the single centre headquarters to the temporary trial ring sites (place of residence of the newly laboratory confirmed EVD case), once they were identified, and conducted all visits at the ring sites until the last visit (Day 84) was completed and the rings were considered closed.

Protocol amendments:

This clinical trial was implemented according to V0.3 of the protocol and its subsequent amended versions, V0.4 (written after the interim analysis) and V0.5.

There were changes in the inclusion/exclusion criteria in Protocol V0.3, V0.4 and V0.5.

Protocol V0.4 (dated 08 July 2015) was implemented following the DSMB meeting of 03 July 2015 (see above).

In addition to clarifications and wording corrections, the other principal changes from V0.3 to V0.4 were:

- Included the decision of the DSMB meeting of 03-Jul-2015 to allow enrolment of adolescents (12 to 18-year-old) and to stop allocation into the delayed arm.
- Included the decision to allow enrolment of children 6-12 years (dependent on safety results, expected 4 weeks later).

Fifty-five protocol deviation reports were completed, which enumerated impact to 819 subjects. Eighteen of the 55 reports also described deviations impacting multiple subjects but did not identify the exact subjects impacted (6 of which described conventions for capturing data in source or CRF, which were applied generally throughout the trial, but did not necessarily impact all subjects).

Seven reports were identified as presenting risk to the subject (or another person's) safety, rights, or privacy.

Trial Monitoring:

Regular monitoring visits at study sites were performed according to ICH GCP by AARSH, an independent Contract Research Organization (CRO) from Senegal, under contract to the Centre for Vaccines Development (CVD) in Mali.

An independent audit (performed by external contractor) was organized by the sponsor (WHO) in Guinea (audit and follow up visit in August 2015 and November 12, 2015) as well as in WHO headquarters, Geneva, Switzerland (23 September 2015).

The scope of the audit was as follows: (i) Sponsor's organization, facilities, equipment, operating procedures, in Guinea; (ii) On site investigations (vaccination and follow-up); (iii) Coordination and synergy with the National Ebola response program; (iv) Data verification, consistency between CRFs and electronic data-base; (v) e-Trial Master File and Investigator Site File.

The objectives of this audit were: GCP compliance of the trial-related activities, with review of provisions regarding: (i) Safety, rights and well-being of participants; (ii) Reliability and credibility of the trial data.

The CSR states that no critical observations were reported and no instances that would cause concern regarding patient safety or the integrity of the trial data were evident.

Numbers analysed

Tables 12 and 13 present the number of participants (denominator) in each group for the different populations used in the analyses.

The primary efficacy analysis (analysis 1^(P)) included all subjects vaccinated in the immediate arm versus all subjects who were eligible and consented on Day 0 in the delayed arm. The secondary analyses compared the following populations' subsets:

- All vaccinated in immediate versus all eligible in delayed (secondary analysis 1^(S1)).
- All eligible in immediate versus all eligible delayed (secondary analysis 2^(S2)).
- All CCCs in immediate versus all CCCs in delayed (secondary analysis 3^(S3)).

Vaccine effectiveness was an estimation of the overall reduction in EVD in rings that were randomized to immediate vaccination compared to those randomized to delayed vaccination.

Table 12. Analyses sets

Populations for analyses:	Immediate	Delayed
Eligible and consented and vaccinated	2119 ^{(P),(S1)}	2041
Eligible and consented on Day 0	2151	1435 ^(P)
Eligible and consented	2151	2539
Eligible	3232 ^(S2)	3096 ^{(S1),(S2)}
All CCCs	4539 ^(S3)	4557 ^(S3)

Table 13. Vaccine effects analyses set and number of cases (within and from 10 days of randomization) per set

	Denominators (ring population)			Numerator (number of EVD)			
	Immediate	Delayed	Non-randomised		Immediate	Delayed	Non-randomised
CCCs	4539	4557	2745	<10 days	26	28	17
				≥10 days	10	22	2
				Total	36	50	19
Eligible	3232	3096	2006	<10 days	20	21	11
				≥10 days	7	16	0
				Total	27	37	11
Consent Day 0	2151	1435	1678	<10 days	11	6	10
				≥10 days	0	10	0
				Total	11	16	10
Consent Day 21	0	1104	0	<10 days	0	0	0
				≥10 days	0	1	0
				Total	0	1	0
Consent day 0, vaccinated	2119	940	1677	<10 days	11	0	10
				≥10 days	0	3*	0
				Total	11	3	10
Consent Day 21, vaccinated	0	1101		<10 days	0	0	0
				≥10 days	0	1*	0
				Total	0	1	0

*4 EVD cases occurred ≥ 10 days after randomization in vaccinated CCCs from the delayed clusters, all occurred < 10 days of vaccination.

Table 13 above also presents the numerators. Endpoints were laboratory confirmed EVD cases in the treatment or control groups. Since EVD cases were confirmed through the Cellule de la Coordination Nationale de Lutte contre la Maladie a Virus Ebola, Republic of Guinea MOH, information on EVD outcome was available for all subjects who had appropriate EVD testing, regardless of their informed consent status.

A total of 105 cases of confirmed EVD were identified during the pilot and main study phases (36 in the immediate clusters, 50 in the delayed clusters, and 19 in the non-randomized clusters).

A total of 71 cases of confirmed EVD less than 10 days after randomization were identified (26 in the immediate clusters, 28 in the delayed clusters, and 17 in the non-randomized clusters).

A total of 34 cases of confirmed EVD occurring 10 days or more after randomization were identified (10 in the immediate clusters, 22 in the delayed clusters, and 2 in the non-randomized clusters).

Vaccine efficacy/effectiveness primary and secondary analyses were performed on populations whose early endpoints (subjects reporting EVD with onset < 10 days from randomization) were removed.

Outcomes and estimation

Attack rates

A total of 105 cases of confirmed EVD were identified during the pilot and post-randomization phase (n=19) and the main study phase (n=86).

The attack rates for the time period < 10 days after randomization vary between 0.5% and 0.8% depending on the population subset. These rates were similar in the immediate vs. delayed vaccination arms, and for those vaccinated vs. not vaccinated. Attack rates were also similar for the comparison of the primary populations' subsets (vaccinated immediate vs. consented Day 0 delayed, respectively 0.5% vs. 0.4%). Thus, there was no effect of vaccination on EVD cases that occurred < 10 days of randomization.

In contrast, no EVD cases occurred ≥ 10 days of randomization in those vaccinated immediately, while 10 cases occurred in the delayed arm consenting on Day 0 subjects. For this primary comparison, attack rates were respectively 0.0% and 0.7% (vaccinated immediate vs. consented Day 0 delayed). Attack rates were similar for subjects assigned to the delayed vaccination group (0.5%) or not vaccinated in the immediate groups (0.6%).

Clustering of the cases

The 20 and 21 cases of EVD that occurred < 10 days of randomization among eligible CCCs involved 9 and 14 clusters, respectively in the immediate and delayed arm. The 7 and 16 cases of EVD that occurred ≥ 10 days of randomization among eligible CCCs involved 4 and 7 clusters, respectively in the immediate and delayed arm. The 10 cases involved in the primary analysis only involved 4 clusters.

Occurrence of EVD in contacts vs. contacts-of-contacts:

There were 27 cases (< 10 days or ≥ 10 days of randomization) in the population used for the primary analysis (vaccinated immediate vs. consented day 0 delayed).

- Of the 11 cases that occurred < 10 days of randomization in subjects vaccinated in the immediate arm, 1/11 was a contact-of-contacts, and 10/11 were contacts (all high-risk contacts).
- Of the 6 cases that occurred < 10 days of randomization in the consenting on Day 0 in the delayed arm, none was contact-of-contacts, and 6/6 were contacts (of which 5 high-risk contacts).

- No case occurred ≥ 10 days of randomization in subjects vaccinated in the immediate arm.
- Of the 10 cases that occurred ≥ 10 days in the subjects consenting on Day 0 in the delayed arm, 3/10 were contact-of-contacts, and 7/10 were contacts (of which 1 high-risk contact).

Of the study population, 20% were contacts and 80% were contacts-of-contacts. In contrast, of all the 27 EVD cases that occurred in the primary analysis population, nearly all (n=23) were contacts (mainly [n=16] high-risk contacts), and only 4 were contacts-of-contacts (3 of them occurred ≥ 10 days). The over-representation of high-risk contacts was even more marked in for the EVD cases that occurred < 10 days after randomization (of 17 cases, 15 high-risk contacts).

Vaccine efficacy against EVD

Ten confirmed EVD cases were observed among 1,429 eligible subjects in the delayed vaccination arm who consented on Day 0, compared to 0 cases among 2,108 eligible subjects in the immediate vaccination arm. Efficacy with V920 was 100%, with 95% CI ranging from 63.5% to 100%; $p=0.0471$ (Fisher's exact test comparing rings) (Column 1 of the table below).

Table 14. Vaccine effect on EVD cases for different comparisons of study population in the V920-010 trial

	Randomized rings*					All rings**			
	1	2	3	4	5	6	7	8	9
	All vaccinated in immediate (A) versus all eligible and consented on Day 0 visit in delayed (B)	All vaccinated in immediate (A) versus all eligible and consented in delayed (B)	All vaccinated in immediate (A) versus all eligible in delayed (B)	All eligible in immediate (A) versus all eligible delayed (B)	All CCCs in immediate (A) versus all CCCs in delayed (B)	All immediately vaccinated (A) versus all CCCs in delayed clusters plus all never vaccinated in immediate or non-randomized (B)	All vaccinated in immediate (A) versus all eligible in delayed plus all eligible never vaccinated in immediate (B)	All contacts and contacts of contacts in immediate (A) versus delayed (B)	All vaccinated in immediate (A) versus all eligible never vaccinated in immediate (B)
Group A									
Subject (clusters)	2108 (51)	2108 (51)	2108 (51)	3212 (51)	4513 (51)	3775 (70)	3775 (70)	7241 (70)	3775 (70)
EVD cases (clusters affected)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)	0 (0)	0 (0)	12 (7)	0 (0)
Attack rate	0%	0%	0%	0.22%	0.22%	0%	0%	0.17%	0%
Group B									
Subject (clusters)	1429 (46)	2533 (47)	3075 (47)	3075 (47)	4529 (47)	7995 (116)	4507 (104)	4529 (47)	1432 (57)
EVD cases (clusters affected)	10 (4)	11 (5)	16 (7)	16 (7)	22 (8)	34 (15)	23 (11)	22 (8)	7 (4)
Attack rate	0.7%	0.43%	0.52%	0.52%	0.49%	0.43%	0.51%	0.49%	0.49%
Vaccine effect									
Vaccine effect and 95% CI†	100% (63.5 to 100)	100% (60.1 to 100)	100% (68.9 to 100)	64.6% (-46.5 to 91.4)	64.6% (-44.2 to 91.3)	100% (77.0 to 100)	100% (79.3 to 100)	70.1% (-4.9 to 91.5)	100% (-51.5 to 100)
p value‡	0.0471	0.0226	0.0045	0.344	0.3761	0.0012	0.0033	0.2759	0.125
* Non-randomized immediate clusters are excluded from this analysis.									
** Randomized and non-randomized clusters allocated to immediate vaccinations are combined.									
† From fitting a β -binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (columns 1, 2, 3, 6, and 7); from Cox proportional hazards model (columns 4, 5, and 8); from signed test (2-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 9).									
‡ From Fisher's exact test (2-sided) (approximate for columns 6 and 7). From sign test (2-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 9).									

To supplement this primary analysis, an additional analysis was performed in all eligible subjects of the delayed vaccination arm who consented at any time. The vaccine effect was 100% (95% CI: 60.1% to 100%); $p=0.0226$ (Column 2 of Table above).

The V920-010 study was designed to enrol 190 rings. The Interim Analysis (IA) was conducted on 90 rings. Although the interim analysis results did not reach the prespecified criterion, randomization in the trial was stopped because it was determined that it would be difficult to define new rings. The decision was made by the DSMB to vaccinate all subsequent subjects immediately. Therefore, the final analysis was conducted on 98 rings following the recommendation of the DSMB to stop random assignment into immediate and delayed vaccination. Thus, the Applicant regards the analysis including only consented subjects based on 98 rings (corresponding to a vaccine efficacy of 100% (95% CI: 63.5% to 100%)) to

represent a final analysis and not an interim analysis. In addition, the population (only consented subjects) utilized in this final analysis differed from that used at the interim analysis (eligible subjects) based on a request from the FDA and reflects a more conservative analysis. Even though a different population was used for the primary vs. the interim analysis, from a statistical perspective multiplicity should be accounted for. Therefore during the procedure the Applicant was asked to provide confidence intervals adjusted for multiplicity leading to a vaccine efficacy of 100% (unadjusted 95% CI: 63.5% to 100%; 95% CI adjusted for multiplicity: 14.4% to 100%) (0 cases in the immediate arm; 10 cases in 4 rings in the delayed arm).

Additional efficacy and effectiveness analyses on EVD

Planned secondary analyses that assess vaccine effectiveness against confirmed EVD and efficacy against death from laboratory-confirmed EVD supported the primary analysis.

Comparing all vaccinated subjects randomly assigned to immediate vaccination versus all eligible subjects assigned to delayed vaccination – the primary analysis in medical literature, demonstrated a vaccine effect of 100% (95% CI: 68.9% to 100%); p=0.0045 (Column 3 of table above).

Other analyses including vaccine effectiveness using a variety of populations, such as all randomized subjects regardless of vaccination status or all clusters irrespective of randomization, suggested trends of a benefit of vaccination (Columns 4-5, 8-9 of table above). It is notable that all cases of EVD among subjects randomized to the immediate arm occurred in the unvaccinated subjects. Furthermore, no subject who received the V920 vaccine developed Ebola disease 10 or more days after vaccination.

Vaccine efficacy for preventing death

The secondary efficacy analyses for preventing EVD deaths are presented in table 15 below. A key comparison was between all vaccinated subjects in immediate arm versus all eligible subjects in delayed arm who consented on Day 0, yielding a vaccine effect of 100% (95% CI: 64.3% to 100%); p=0.0471. Results from other populations were consistent with analyses on EVD endpoint.

Table 15. Vaccine Effect on EVD Death for different comparison of study population

	All clusters**				Randomized clusters***			
	All vaccinated in immediate (A) versus all delayed plus all never vaccinated in immediate (B)	All vaccinated in immediate (A) versus all eligible in delayed plus all eligible never vaccinated in immediate (B)	All contacts and contacts of contacts in immediate (A) versus delayed (B)	All vaccinated in immediate (A) versus all eligible never vaccinated in immediate (B)	All vaccinated in immediate (A) versus all eligible and consented on Day 0 visit in delayed (B)	All vaccinated in immediate (A) versus all eligible in delayed (B)	All eligible in immediate (A) versus delayed (B)	All CCCs in immediate (A) versus all CCCs in delayed (B)
Group A								
Subject (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
EVD deaths (clusters affected)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)	2 (2)
Risk of EVD-specific death	0%	0%	0.03%	0%	0%	0%	0.03%	0.04%
Group B								
Subject (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
EVD deaths (clusters affected)	17 (8)	13 (7)	15 (6)	1 (1)	8 (4)	12 (6)	12 (6)	15 (6)
Risk of EVD-specific death	0.21%	0.29%	0.33%	0.07%	0.56%	0.39%	0.39%	0.33%
Vaccine effect								
Vaccine effect and 95%CI†	100% (54.8 to 100)	100% (67 to 100)	92.3% (52.9 to 98.8)	100% (-3800 to 100)	100% (64.3 to 100)	100% (62.6 to 100)	92% (23.4 to 99.2)	88.8% (27.6 to 98.3)
p value‡	0.0257	0.0426	0.0588	1	0.0471	0.0102	0.0525	0.148

*For the secondary analysis, endpoints are confirmed EVD deaths with onset of symptoms at least 10 days post-randomization.

** Randomized and non-randomized allocated to immediate vaccination are combined.

***Non-randomized immediate clusters are excluded from this analysis.

†From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (columns 1, 2, 5 and 6).

‡From Cox proportional hazards model (column 3, 7 and 8). From signed test (2-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4).

§ From Fisher’s exact test (2-sided) (approximate for columns 1 and 2). From sign test (2-sided): probability of observing endpoints in control groups among treatment-control mismatched pairs and under the null hypothesis that the vaccine has no efficacy (column 4).

Other efficacy analysis

The incidence of EVD before the 10-day post-vaccination cut-off, in the immediate arm versus the delayed arm, is presented in table 16 below. This data is based on the final primary efficacy analysis population.

Table 16. V920-010: EVD incidence after vaccination before and after the 10-day post-vaccination cut-off: all vaccinated in immediate vs. all eligible in delayed (primary analysis)

Vaccinated	Group	EVD Cases before Vaccination (Rings)	EVD Cases <10 days Postvaccination (Rings)	EVD Cases ≥10 days Postvaccination (Rings)
Vaccinated	Immediate	NA	11 (4)	0 (0)
	Delayed	13 (8)	3 (1)	0 (0)
	Not Randomized	NA	10 (7)	0 (0)
EVD = Ebola virus disease; NA = not applicable				

Source: World Health Organization data

During Days 0-9 post-vaccination, 11 EVD cases occurred in the immediate arm and 3 in the delayed arm (symptom onset on Days 0, 6, or 6 post-vaccination), and 10 cases in the non-randomized group.

From randomization to Day 21 in the delayed arm, 13 cases were reported, 6 cases with onset from randomization to Day 9, and 7 cases with onset from Day 10 to Day 21 following randomization.

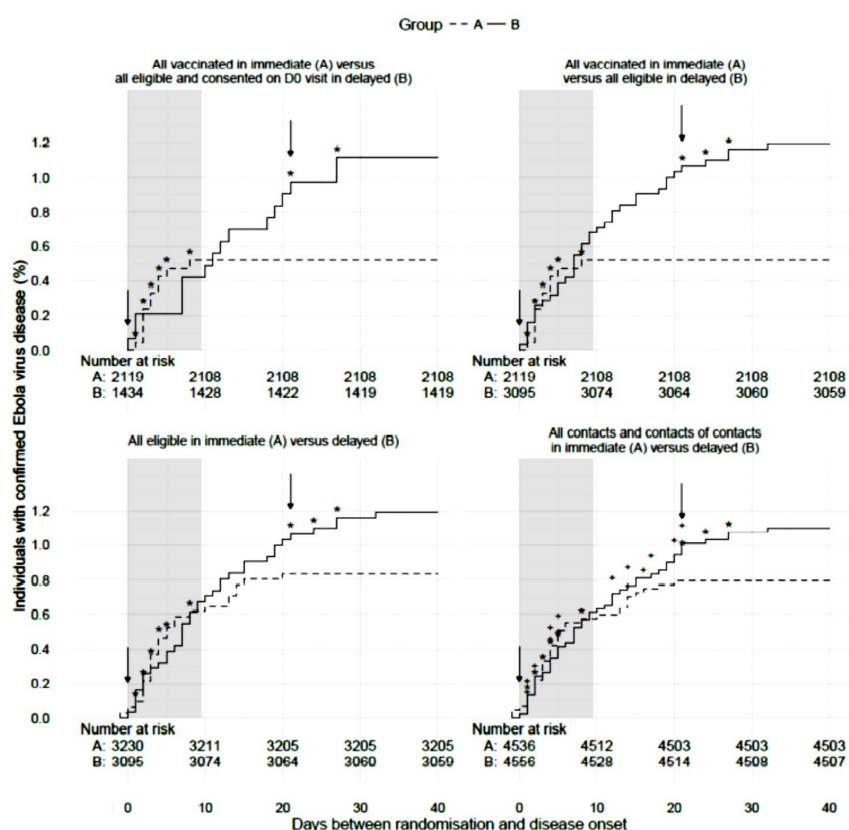
Kaplan-Meier curves

Kaplan-Meier curves show that the incidence of EVD cases in the first 10 days following vaccination or enrolment was similar in the immediate, delayed, and nonrandomized clusters (Figure 2 below). However, no EVD cases occurred ≥10 days post-vaccination in any group.

No EVD cases after 32 days post-randomization were identified in randomized and non-randomized clusters in vaccinated and non-vaccinated individuals, suggesting that V920 might have contributed to the interruption of Ebola transmission.

Overall, the assessment of the durability of protection in this design is limited. Aligning the interval of efficacy assessment in both immediate and delayed vaccination arms allows for the conclusion that duration of protection is of at least 31 days.

Figure 3. Kaplan-Meier Curves for laboratory-confirmed EVD cases in various study populations for the randomised evidence in the V920-010 Trial



Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of Efficacy for trial V920-010

Title: A Randomized Trial to Evaluate Ebola Vaccine Efficacy and Safety in Guinea, West Africa.	
Study identifier	V920-010; the Guinea ring vaccination, open-label, cluster-randomized trial; Ebola Ça Suffit!
Design	Field-based, Phase 3, open-label, cluster-randomized, controlled ring vaccination trial, designed to evaluate the efficacy, effectiveness and safety of 1 dose of V920 in the prevention of EVD when implemented as ring vaccination. A cluster (ring) consisted of all contacts and contacts-of-contacts (CCCs) of the index case (new case of a laboratory-confirmed EVD in the trial area). Clusters were randomized to the immediate arm or to the delayed (control) arm in a 1:1 ratio. The trial was conducted in Guinea, during the 2014-2016 West African Ebola outbreak.

	Duration of main phase:	Subjects were followed respectively 84 & 105 days (immediate and delayed arms).	
	Study start/end:	Recruitment in the pilot phase occurred from March 23 to April 1, 2015. The randomization was conducted from April 1 (first subject enrolled) to July 21, 2015 (last subject enrolled). After July 27, all consenting subjects received the vaccine immediately. Last subject last visit (LSLV) was on 20-JAN-2016.	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	Not applicable	
Hypothesis	Superiority		
Treatments groups	Immediate arm	Vaccination with 1 dose of V920, 1-2 days after randomization, 4539 CCCs (3232 eligible) in 51 clusters.	
	Delayed arm	Vaccination with 1 dose of V920, 21 days after randomization: 4557 CCCs (3096 eligible) in 47 clusters.	
Endpoints and definitions	Primary endpoint	cEVD	Confirmed EVD: (i) Any probable or suspected case from which a blood sample taken was laboratory confirmed as positive for EVD, or (ii) Any deceased individual with probable EVD, from which a post-mortem sample taken within 48 hours after death was laboratory confirmed as positive for EVD. Laboratory confirmation was obtained through the local laboratories of the national Ebola surveillance system by detection of virus RNA using real time reverse transcriptase-polymerase chain reaction (RT-PCR).
	Secondary endpoint	pEVD	Probable EVD: Any suspected case evaluated by a clinician OR any person who died from suspected EVD and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease.
	Secondary endpoint	sEVD	Suspected EVD: Any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a suspected, probable or confirmed EVD case, or a dead or sick animal OR any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia/loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccup; OR any person with unexplained bleeding OR any sudden, unexplained death.
Database lock	Data Base Lock: Data Base Lock: 20-APR-2016		
Results and Analysis			
Analysis description	Primary Analysis, efficacy against cEVD		

Analysis population and time point description	All vaccinated in immediate versus all eligible and consenting on Day 0 in delayed. This population of analysis was not pre-specified. cEVD with onset 10-31 days after randomization.		
Descriptive statistics and estimate variability	Treatment group	Immediate arm	Delayed arm
	Number of subject	2108 (51 clusters)	1429 (46 clusters)
	cEVD 10-31 days Attack rate	0.00%	0.70%
	Number of subjects (rings) with cEVD 10-31 days	0 (0)	10 (4)
Effect estimate per comparison	cEVD 10-31 days	Comparison groups	Immediate vs delayed arms
		Vaccine Efficacy	100%
		95% CI	63.5% to 100%
		P-value (Fisher's exact test, 2-sided)	0.0471*
Notes	The populations of analysis and the period for censoring the data (<10 days after randomisation) were not pre-specified. * The significance level at interim was $\alpha = 0.0027$		
Analysis description	Secondary analysis, efficacy against cEVD		
Analysis population and time point description	All vaccinated in the immediate arm vs all vaccinated in the delayed arm. cEVD with onset 10-31 days after randomization.		
Descriptive statistics and estimate variability	Treatment group	Immediate arm	Delayed arm
	Number of subject	2108 (51 clusters)	3075 (47 clusters)
	cEVD 10-31 days Attack rate	0.00%	0.52%
	Number of subjects (rings) with cEVD 10-31 days	0 (0)	16 (7)
Effect estimate per comparison	cEVD 10-31 days	Comparison groups	Immediate vs delayed arms
		Vaccine Efficacy	100.0%
		95% CI	68.9% to 100.0%
		P-value (Fisher's exact test, 2-sided)	0.0045
Notes	The period for censoring the data (<10 days after randomisation) was not pre-specified.		
Analysis description	Secondary analysis, effectiveness against cEVD		
Analysis population and time point description	All eligible in the immediate arm vs all eligible in the delayed arm. cEVD with onset 10-31 days after randomization.		
Descriptive statistics and estimate variability	Treatment group	Immediate arm	Delayed arm
	Number of subject	3212 (51 clusters)	3075 (47 clusters)

	cEVD 10-31 days Attack rate	0.22%	0.52%
	Number of subjects (rings) with cEVD 10-31 days	7 (4)	16 (7)
Effect estimate per comparison	cEVD 10-31 days	Comparison groups	Immediate vs delayed arms
		Vaccine Effectiveness	64.6%
		95% CI	-46.5% to 91.4%
		P-value (Fisher's exact test, 2-sided)	0.344
Notes	The period for censoring the data (<10 days after randomisation) was not pre-specified.		
Analysis description	Secondary analysis, effectiveness against cEVD		
Analysis population and time point description	All contacts-of-contacts (CCCs) in the immediate arm vs all CCCs in the delayed arm. cEVD with onset 10-31 days after randomization.		
Descriptive statistics and estimate variability	Treatment group	Immediate arm	Delayed arm
	Number of subject	4513 (51 clusters)	4529 (47 clusters)
cEVD 10-31 days Attack rate		0.22%	0.49%
	Number of subjects (rings) with cEVD 10-31 days	10 (5)	22 (8)
Effect estimate per comparison	cEVD 10-31 days	Comparison groups	Immediate vs delayed arms
		Vaccine Effectiveness	64.6%
		95% CI	-44.2% to 91.3%
		P-value (Fisher's exact test, 2-sided)	0.3761
Notes	Intention-to-treat analysis. The populations for this analysis was pre-specified. This analysis is referred to as effectiveness analysis. The period for censoring the data (<10 days after randomisation) was not pre-specified.		
Analysis description	Secondary analysis: Efficacy against death by cEVD.		
Analysis population and time point description	All vaccinated in immediate versus all eligible and consenting on Day 0 in delayed. cEVD with onset 10-31 days after randomization.		
Descriptive statistics and estimate variability	Treatment group	Immediate arm	Delayed arm
	Number of subject	2108 (51 clusters)	1429 (46 clusters)
cEVD 10-31 days Attack rate		0.00%	0.56%
	Number of subjects (rings) with cEVD 10-31 days	0 (0)	8 (4)
Effect estimate per comparison	cEVD 10-31 days	Comparison groups	Immediate vs delayed arms

		Vaccine Efficacy	100.0%
		95% CI	64.3% to 100.0%
		P-value (Fisher's exact test, 2-sided)	0.0471
Notes	Intention-to-treat analysis. The populations for this analysis was pre-specified. This analysis is referred to as effectiveness analysis. The period for censoring the data (<10 days after randomisation) was not pre-specified.		
Analysis description	Other secondary analysis		
Efficacy against pEVD	Analysis not done (nearly all cases were confirmed).		
Efficacy against sEVD	Analysis not done (nearly all cases were confirmed).		
Effectiveness in the prevention of cEVD after 84 days of monitoring.	This analysis was part of the objectives but was not done. The analysis seems not consistent with the study design (see LOQ).		

Analysis performed across trials

The Applicant plans to pool the immunogenicity data across trials in a cross-over immunogenicity analysis including the data from the phase 2/3 trials, which used validated GP-ELISA and PRNT assays. Such analysis will be submitted post-authorisation.

Clinical studies in special populations

No trials have been performed in older adults.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

V920-010 is a field-based, Phase 3, open-label, cluster-randomized, controlled, ring vaccination trial, designed to evaluate the efficacy, effectiveness and safety of 1 dose of V920 in the prevention of EVD when implemented as ring vaccination. The study sponsor was WHO. The study was conducted in Guinea during the 2014–2016 outbreak of EVD in West Africa. A cluster (ring) consisted of all contacts and contacts-of-contacts (CCCs) of the index case (new case of a laboratory-confirmed EVD in the trial area). Clusters were randomized to immediate arm (vaccination 1-2 days after randomization) or delayed (control) arm (vaccination 21 days later) in a 1:1 ratio. Subjects were followed from the constitution of the ring up to 84 days after the vaccination through study visits by the trial's team. The MoH/WHO surveillance team visited the subjects up to 21 days after the contact (contact tracing). New cases of EVD admitted to the Ebola Treatment Centres (ETC) were reported by the MoH/WHO centre. EVD cases were confirmed by PCR.

The ring vaccination design is an innovative alternative in an outbreak setting to allow for a pragmatic conduct. Although more prone to biases compared to an individually randomised trial, this design was much more likely to yield robust data on the efficacy of the vaccine despite the low and declining incidence.

Overall, the definitions of contacts and contact-of-contacts and eligibility criteria are endorsed. A new cluster was defined if at least 60% of the CCCs were not enumerated in a previous cluster. The

geographical distribution of the rings suggest that important overlaps may have occurred in the largest prefectures, however individuals geographically located in several rings were assigned to and vaccinated as part of the first ring in which they were included. As there is no data to quantify the extent of geographical overlap between clusters, biases due to this overlap cannot be excluded. For example, it is questioned whether the proportion of subjects who were exposed to 2 or more index cases was comparable between the immediate and the delayed arms. The impact of potential bias remains uncertain as no sensitivity analyses accounting for overlapping clusters could be performed.

Objectives and endpoints

The aim of the study was to assess efficacy (primary analysis) over a defined period of time of 21 days and effectiveness over a broader period of 84 days after randomisation.

Asymptomatic and pauci-symptomatic cases were described during the West African outbreak. However, the study was designed to detect cases of EVD using the standard WHO case definition, with fever as key symptom, and not to detect possible subclinical cases of EVD. The use of confirmed EVD as primary efficacy endpoint is consistent with WHO guidelines. For this trial, only RT-PCR assay was used for laboratory confirmation of Ebola infection.

Blinding

The V920-010 trial is open-label. The EVD case detection in the field was not blinded to the subject's allocation status. The direction and magnitude of any resulting bias is unknown. The group allocation information was not communicated to the national surveillance lab staff.

Statistical analyses

The incidence of EVD was compared between the 2 arms over defined time periods measured from the date of first vaccination within the ring for subjects in the immediate arm, and the date of first enrolment within the ring for subjects in the delayed vaccination arm.

Cases of Ebola occurring <10 days after randomization/enrolment were censored. The time after which the vaccine is perceived to provide full protection in the vaccinees was selected by default to be at least 10 days after randomization, taking account of both the incubation time and the putative vaccine-response period. The 10-day censoring period was specified prior to the conduct of the efficacy analyses with the intention to minimize the post-exposure effect in the efficacy analyses. A protective effect of V920 against EVD cases was expected in contacts-of-contacts. In practice, the effect was mainly seen in contacts, which could include post-exposure effect.

The populations compared for the primary efficacy analyses were not pre-specified. The primary efficacy interim analysis compared all subjects vaccinated in the immediate arm versus all subjects eligible in the delayed arm. After that analysis was published, the FDA requested that the primary efficacy analysis focus on all subjects vaccinated in the immediate arm compared to all subjects who consented on the Day 0 visit in the delayed arm. This approach is considered appropriate as the subset consenting on Day 21 is highly biased in particular because it discards subjects who presented EVD during the relevant period (i.e. 0 to 21 days). The secondary analysis estimating the overall ring vaccination effectiveness in protecting all CCCs was pre-specified. It is considered as the intention-to-treat analysis and the less susceptible to selection bias, hence the most valid.

Statistical methods were only very briefly defined in the protocol and SAP. Furthermore, the methods used to derive the results for the primary endpoint were not pre-specified in the protocol and SAP, however the applied test is considered to be a conservative approach.

The Sponsor planned to conduct an interim analysis after approximately 100 clusters. The interim analysis results were not significant based on the pre-planned multiplicity adjustment, but randomization

in the trial was stopped by the DSMB because of the low probability of being able to recruit substantial numbers of additional rings (given the declining number of cases of Ebola virus disease in the country). The Applicant presented these data in the CSR without multiplicity adjustment and conducted one post-hoc analysis, i.e. the interim analysis, which was used as primary analysis using the full alpha. Using the full alpha at interim after stopping the trial is not considered a suitable approach as it would always allow rejecting the null hypothesis at the full alpha level at interim. This approach is hence not considered sufficient to control the type 1 error rate. The study is considered to have failed to meet its primary endpoint; an adjusted confidence interval was therefore also provided in the SmPC.

All analyses were done at the cluster level, and hence the high intra-class correlation coefficient (ICC) was included in the analyses. A Bayesian model with Beta prior for probability of EVD and treatment effect as only covariate was used. The underlying assumptions and consequences of the Bayesian model are uncertain. Stratification factors were not taken into account in any of the analysis. As using stratification factors in the analysis model usually helps to reduce heterogeneity, the approach taken is considered to be conservative and is hence acceptable.

Conduct of the study

The trial was conducted in the region of Basse-Guinée, a coastal area of Guinea, and comprised 7 prefectures in Guinea (including Conakry). This area was the only area of Guinea in which cases of EVD were confirmed at the time of the start of the study. Two prefectures in Sierra Leone were added during the non-randomised phase. After the randomisation phase, the Protocol was amended to include children and adolescents from 6 years of age.

The trial team headquarters was located in Conakry. The trial's field teams travelled from the headquarters to the temporary trial ring sites to conduct the visits. This trial was performed in particularly challenging logistical circumstances.

Several concerns about GCP potential compliance issues which may impact on data accuracy were raised during the assessment: (i) Inconsistencies between protocol, CSR, published papers; (ii) Monitoring was regularly performed at the Sponsor's Coordination Center in Conakry, but study sites were not monitored; (iii) One independent audit organized by the Sponsor in August 2015 (after most subjects completed the randomisation phase) raises several major GCP concerns. In particular: operations of the activity of the sponsor and the investigator are not described in a consolidated manner in the study procedures, inconsistencies were found between the database and the source documents including with respect to SAEs.

Considering the limitations of the trial given the specific circumstances in which it was conducted (i.e. in Africa during an Ebola outbreak), the lack of study sites available for an inspection, the unmet medical need for a prophylactic intervention against EVD, and given the context of the ongoing WHO-declared Public Health Emergency of International Concern (PHEIC) in the Democratic Republic of Congo (DRC), the request for a GCP inspection has been waived.

Efficacy data and additional analyses

The study randomised 4539 CCCs (3232 eligible) in 51 clusters, 4557 CCCs (3096 eligible) in 47 clusters over approximately 4 months while the epidemic was ending.

Baseline data

Both arms were roughly distributed in a balanced way over time although a slightly higher proportion of the immediate clusters was recruited during the first third of the period as compared to the delayed clusters (41% vs. 36%).

The median size of the clusters was similar in both arms (80 CCCs in immediate vaccination groups and 81 CCCs in delayed vaccination groups). However, the cluster size was not balanced across arms for the primary analysis (average ring size in terms of participants who consented prospectively was 42.2 and 30.5 respectively in the immediate and delayed arms). This may bias the cluster-level analysis but not in favour of the vaccine.

The proportion of eligible CCCs was approximately 70% for both arms, the main reason for non-eligibility being age below the lower limit (6 years). Eligible CCCs who were cluster-randomized to delayed clusters had two opportunities to consent. In this arm, 31% of CCCs consented on Day 0 (versus 47% in the immediate arm), and 24% of the CCCs consented on day 21.

Demographic data for the subsets of eligible subjects who consented on Day 0 is comparable across arms, and the same applies for the proportion of contacts-of-contacts (80%) vs. contacts (20%), supporting the primary analysis. The proportion of high-risk contacts was however slightly different (15% vs 12% respectively in the immediate and delayed arms). The subsets used for the (primary) analyses could differ with respect to other important characteristics predicting the EVD, such as the time interval between the onset of symptoms in the index case and the context, and the nature and frequency of the contacts.

Numbers analysed and attack rates of EVD cases

A total of 105 cases of confirmed EVD were identified during the pilot and post-randomization phase (n=19) and the main study phase (n=86, of which 36 pertained to the immediate clusters and 50 to the delayed clusters). All confirmed EVD cases used for the main outcome were reaffirmed by repeat testing at the European Mobile Laboratory (EML).

During the randomization phase, most cases of confirmed EVD occurred <10 days after randomization¹ (70% and 50% in the immediate and delayed arms), reflecting the fact that nearly all cases occurred in (high-risk²) contacts who were likely already exposed to infection before randomization. There was no effect of vaccination on EVD cases that occurred <10 days after randomization (attack rates 0.4-0.8% whatever the subset). In contrast, no EVD case occurred ≥10 days after randomization in those vaccinated immediately, while 10 cases occurred in the delayed arm in those consenting on Day 0. For this primary comparison, attack rates were respectively 0.0% and 0.7%. Attack rates were similar for subjects assigned to the delayed vaccination rings (0.5%) or not vaccinated in the immediate rings (0.6%).

Of the study population, 20% were contacts and 80% were contacts-of-contacts. In contrast, of all the 27 EVD cases (10 cases that occurred <10 days and 17 cases that occurred ≥10 days) which occurred in the population used for the primary analysis, nearly all (n=23) were contacts (of these, 16 were high-risk contacts), and only 4 were contacts-of-contacts (3 of them occurred ≥10 days). Thus, as expected, there was an overrepresentation of (high-risk) contacts amongst EVD cases, especially in EVD case that occurred <10 days from randomisation.

There was no EVD case that occurred ≥10 days post-vaccination (i.e. ≥31 days after randomisation in the controls) among the 5,837 subjects who received the V920 vaccine in all 117 rings, both randomized (immediate, delayed) and non-randomized. In the delayed arm, 4 cases of EVD ≥10 days post-randomization were reported in vaccinees, but all occurred within 10 days of vaccination.

Efficacy results

¹ for the delayed arm, vaccination is 21 days after randomisation. Thus, when it is referred to <10 after randomisation, the delayed (control) arm was not yet vaccinated.

² high risk contacts were defined as individuals in close contact with a patient

The V920 vaccine demonstrated to be efficacious after a single IM administration at the intended dose of 2×10^7 pfu, in preventing EVD in the studied population. The primary analysis shows a VE of 100% (95%CI: 63.5 to 100% and p-value 0.0471 without multiplicity adjustment; adjusted 95%CI: 14.4 to 100% based on 0 cases in the immediate arm and 10 cases in 4 rings in the delayed arm). Randomization was stopped after an interim analysis with a $p=0.0036$ that did not meet the pre-specified alpha level of 0.0027. The final analysis was conducted on 98 clusters and the interim analysis on 90 clusters, thus formally only confidence intervals and p-values adjusted using the pre-planned alpha-spending approach should be reported.

As the estimation of VE was based on only 4 clusters with 10 confirmed EVD cases ≥ 10 days after randomization, the result is formally not statistically significant and confidence intervals are very wide. This adds uncertainty regarding the actual level of protection induced by the vaccine.

A secondary analysis to include all eligible subjects in the delayed arm yielded consistent results, except the 95%CI lower bound changed to 68.9%. Furthermore, preplanned secondary analyses on EVD death are consistent with the primary analysis.

The secondary vaccine effectiveness analyses comparing all CCCs (i.e., including non-eligible and non-vaccinated subjects, ITT analysis) or comparing all eligible subjects indicates trends of vaccine benefit but was statistically inconclusive. In this particular trial, the ITT analysis leads to the overall vaccine effectiveness, by comparing the cluster-level incidence in immediately vaccinated clusters (including all CCCs who did not receive the vaccine) versus delayed clusters. The overall vaccine effectiveness is a valuable public health measure reflecting the overall utility of the strategy.

Efficacy was found in a population mixing contacts and contacts-of-contacts. Of the 10 cases included in the primary analysis after the censored period of 10 days post-vaccination, 7 were contacts and 3 were contacts-of-contacts.

Whilst it is considered that vaccine efficacy is demonstrated despite the limitations, it is difficult to differentiate any effect of pre-exposure vs. post-exposure prophylaxis (PEP) because the trial was not designed to assess this. The robustness of the data in favour of a 'pure' pre-exposure effect is hampered by the limited number of cases that occurred in contacts-of-contacts (3 cases vs. 7 cases in contacts) of the yet-to-be-vaccinated delayed (control) arm. However, these data are consistent with the demonstration of protection that was shown in the NHP model.

Median time from symptom onset to hospitalization/isolation in the index cases was approximately 4 days in both arms, which is consistent with the literature, and median time from symptoms onset in the index case to randomization was 10-11 days. At randomisation, 59% and 68% of the index cases had died (immediate and delayed respectively). This shows that contacts, especially those at high-risk, were likely already exposed since several days when vaccinated, and thus may already have contracted the infection when vaccinated (average incubation period for Ebola is 8-10 days [min-max 2-21 days]). As underlined in the CSR, EVD cases in contacts may not have been fully averted unless there was a post-exposure prophylactic effect from the vaccine. However, since vaccination had an effect on EVD with onset >10 days post-randomization period and not before, the vaccine may have no effect when administered late after exposure.

Data for PEP in the context of laboratory and health-care workers in Europe/US is very limited. Seven cases were reported by the Applicant, with varied potential exposures to Ebola, and they were given V920 around 2 days after the accident. None developed evidence of Ebola virus infection or disease. The nominal dose used was ranging from 5×10^7 pfu/mL to $\geq 1 \times 10^8$ pfu/mL, thus in the range of the doses used in the trials. In contrast with preventive protection, there are very limited NC data on post exposure effects. Only a small NC challenge study in rhesus macaques suggests post-exposure efficacy.

Duration of protection

Given the trial's design, efficacy/effectiveness was studied only over a short period of approximately three weeks (10 to 31 days post-randomization). The duration of the vaccine's protective effect in the prevention of EVD is thus unknown. In addition, data from NHP challenge studies on the potential durability of V920 in protecting against EBOV are considered limited at this time (see section 2.3). Data from a NHP study showed only partial protection (<50%) at Month 3 after a single IM dose of V920, and interestingly unprotected vaccinated animals still had substantial amounts of antibodies measured by ELISA and PRNT50. Given the existing NHP data, and especially the current unknowns about both the specific mechanism of protection against EVD and a protective antibody titre, caution needs to be exercised to infer the V920 vaccine protection duration based on the immunogenicity data. It is important that more data is collected in order to understand duration of protection and need for booster doses in the context of the ongoing and future Ebola outbreaks.

Limitations of the ring vaccination trial data

Many sources of biases are present, which are an integral part of the uncertainties around the results: informed consent given based on the knowledge of the assigned group; potential failures in contact tracing; lack of clarity or inconsistencies in case detection and matching processes; potential differences in exposure to study teams during the primary endpoint ascertainment period with a possible impact on the knowledge and behaviour. The impact and direction of potential biases is not known.

The intra-class correlation coefficient (ICC) was unexpectedly high due to the clustering of 6 confirmed endpoint EVD cases in one of the rings. This shows that specific transmission pathways occurred at the local level. The impact of the lack of independency of EVD events is a loss of power, but also possible biases due to imbalance between arms as specific chains of transmission may have occurred at the level of a few rings.

Although it is currently not known which epitopes are responsible for the immune protective responses, no data suggest that V920 is not efficacious against all strains of Zaire ebolavirus. Immunogenicity of V920 suggests that the immune responses are at least as robust in subjects living in non-endemic regions as in endemic regions. It is unlikely that V920-induced immune response will be impaired by pre-existing anti-VSV immunity. Based on limited data, pre-existing immunity to Ebola virus defined by the selected cut-off does not appear to have a negative impact on the immunogenicity of V920. Thus, there is a priori no rationale to anticipate lower vaccine efficacy in EU subjects (non-endemic) compared to African subjects from endemic countries.

Limitations remain in terms of the extrapolation of efficacy data obtained in a ring vaccination context to a prophylactic vaccination context.

Given the important limitations of the currently available efficacy data, and in the absence of a correlate of protection, there is a need to generate additional data to further confirm the vaccine's clinical effect. It will not be possible to prospectively evaluate the efficacy of V920 in EU subjects in a future randomized clinical trial. Thus, coordinated efforts to generate vaccine effectiveness data from contexts with long-lasting or recurrent outbreaks are essential.

2.5.3. Conclusions on the clinical efficacy

In combination with non-clinical data, the results of the pivotal V920-010 ring vaccination trial "Ebola Ça Suffit" provided evidence that a single IM dose of the V920 vaccine at a concentration of 2×10^7 pfu is efficacious to prevent EVD in adults at risk of infection during an outbreak setting.

However, uncertainties remain as to the actual level of protection, the duration of protection and the type of protection (pre- or post-exposure prophylaxis) given the methodological limitations and the exceptional circumstances experienced during a declining Ebola epidemic as discussed above.

The findings present many important limitations in terms of internal validity and precision of the efficacy estimate. In addition, data may lack the reliability usually expected from a pivotal randomised placebo-controlled trial, which however was unavoidable given the exceptional circumstances in which the trial was conducted and its alternative design.

The CHMP considers the following measures necessary to address the limitations related to efficacy data:

- there is limited data in HIV-infected individuals. Immunogenicity will be further investigated in these subjects in study V920-015 (ACHIV);
- there is limited data on duration of protection and on long term follow up data. Duration of immunogenicity will be addressed in study V920-016 (PREVAC), in study V920-009 (PREVAIL) and in study V920-005 (Geneva).
- effectiveness data obtained by partners in future outbreaks should be submitted as they become available post-authorisation.

Recommendations for future clinical development

- The final study report for study V920-013 should be submitted as soon as available.
- The final study reports for study V920-018 (efficacy and safety in frontline workers in Guinea, part B of the efficacy trial V920-010) should be submitted as soon as available.

2.6. Clinical safety

Patient exposure

The clinical development program to assess safety consisted of 12 trials mostly blinded, but also open label trials. 8 Phase I trials and 4 Phase II and III trials were conducted. These trials were designed and conducted independently by a number of different sponsors in the same timeframe in response to the Ebola outbreak in 2014.

A total of 15,997 adult subjects were vaccinated with V920 in the 12 clinical trials (see table below); 15,399 of these subjects received 2×10^7 plaque forming units (pfu)/dose or higher of V920. Safety was evaluated in all trials. The trials also included approximately 536 eligible, consented adults ≥ 65 years of age, 234 children 6 to 17 years of age, as well as 278 women who were incidentally found to be pregnant during the clinical trials and 22 HIV-positive individuals.

The phase 2/3 placebo-controlled randomized trials (Protocol 009 and Protocol 012) comprised 500 African subjects of Liberia and 1061 subjects of US, Spain and Canada.

Table 18. Summary of Exposure to V920 by Study (Protocols: 001, 002, 003, 004, 005, 006, 007, 008, 009, 010, 011, and 012)

Study	V920 < 2×10^7 pfu n	V920 $\geq 2 \times 10^7$ pfu n	V920 Total	Placebo
Blinded population				
Protocol 001	10	20	30	9
Protocol 002	10	20	30	9
Protocol 003	30		30	10
Protocol 004	323	95	418	94
Protocol 005	86	16	102	13
Protocol 009		500	500	498

Study	V920<2x10 ⁷ pfu n	V920≥2x10 ⁷ pfu n	V920 Total	Placebo
Protocol 012		1061	1061	133
Total	459	1712	2171	766
Open-label Population				
Protocol 006	20	10	30	
Protocol 007	99	16	115	
Protocol 008	20	20	40	
Protocol 010		5642	5642	
Protocol 011		7998	7998	
Total	139	13686	13825	
Overall	598	15398	15996	766

Adverse events

The trials were conducted in different geographical regions (e.g., Africa only vs Europe/North America only) and under different circumstances (e.g., outbreak vs non-outbreak, community vs clinical settings), and used varying methods for data collection (e.g., phone contact with subjects vs in-person visits). The trials were not designed or conducted by the various sponsors with the final objective of data integration among them. Consequently, the datasets could not be properly harmonized and integrated to provide a meaningful and interpretable integrated dataset. It was feasible to integrate SAE data from blinded trials because of the more uniform collection methods for SAEs across trials. SAE data from open-label trials were not included in this integration, as unblinded safety assessments are potentially subject to bias.

Data from the 2 large, randomized, double-blinded, placebo-controlled Phase 2 and 3 trials, V920-009 and V920-012, provide the basis of the primary safety assessment for V920. Data from the 2 large open-label trials, V920-010 and V920-011, as well as the 8 Phase 1 trials, provide supportive safety information.

The majority of subjects who received V920 in each of the Phase 1 blinded trials experienced solicited injection-site AEs (43.1% to 86.7%, V920 Combined Dose groups) and systemic AEs (59.6% to 98.3%, V920 Combined Dose groups) through 14 days post-vaccination, and the proportions of V920 recipients who reported AEs were higher compared with subjects who received placebo ([10.6% to 33.3%] and [33.3 to 100%], respectively). Within the V920-groups in the different trials a heterogeneous reporting rate from 15% to 50% for arthralgia was observed. Myalgia, objective fever, and subjective fever were reported with a higher incidence in the V920 groups compared to placebo groups. Objective fever was generally reported as mild in intensity in the V920 Phase I blinded trials, but 3 subjects experienced severe objective fever.

In each of the V920 Phase 1 open-label trials, the most commonly reported solicited injection-site AE through 14 days post-vaccination in the 2×10^7 pfu/dose V920 group was injection-site pain. The majority of solicited injection-site AEs was reported within the first day (≤ 24 hours) following vaccination. The median durations of injection-site pain, redness/erythema, and swelling reported for the 2×10^7 pfu/dose V920 group ranged from 1.5 to 3.0 days, 1.0 to 3.0 days, and 1.0 to 8.0 days, respectively.

In each of the V920 Phase 1 open-label trials, the most commonly reported solicited systemic AEs in the 2×10^7 pfu/dose V920 group through 14 days post-vaccination were headache (50.0% to 60.0%), fever (V920-006; reported as pyrexia in V920-007 and objective fever in V920-008) (30.0% to 56.3%), fatigue (10.0% to 55.0%), myalgia (12.5% to 70.0%), and arthralgia (10.0% to 25.0%).

Unsolicited systemic AEs associated with lab abnormalities that were reported in the V920 Phase 1 blinded trials were generally not reported in the open-label trials. Only 1 adult subject in the 2×10^7 pfu/dose

V920 group of the V920-007 trial reported an AE of abnormal hepatic function. The majority of vaccine-related unsolicited systemic AEs were mild to moderate in intensity. The only severe vaccine-related unsolicited systemic AEs reported for subjects in the 2×10^7 pfu/dose V920 group was malaise and muscle tightness (in the Phase I trial V920-006).

Phase 2/3 trials

Injection-site reactions

The main studies to evaluate non-serious AEs are the field-based study V920-009 and the Applicant-sponsored study V920-012, both double-blinded and placebo-controlled and respectively comprised 498 African subjects of Liberia and 798 subjects in US, Spain and Canada.

In the V920-009 trial, subjects were prompted at each safety follow-up visit to report injection-site reactions, which were defined as a composite term of injection-site pain/tenderness or local reaction (defined as erythema or swelling, with severity grades: mild – moderate –blistering – ulceration/necrosis/potentially life threatening). All subjects who experienced injection-site reaction reported injection-site pain, and few reported local reactions at any time point (30 minutes, Week 1, or Month 1). Injection-site pain was reported for 34.0% and 11.2% of subjects in the V920 and placebo groups, respectively, at any time point, and was most prevalent at the Week 1 visit (30.7% and 6.8% of subjects in the V920 and placebo groups, respectively). The maximum intensities for AEs of injection-site pain and local reaction at any time point were mild or moderate.

In the V920-012 trial, subjects were prompted to report the injection-site AEs of erythema, pain, and swelling on the vaccination report card (VRC) on Days 1 to 5 post vaccination. A majority (72.3% to 70.4%, respectively) of subjects in the V920 Combined Lots (2×10^7 pfu/dose) and High Dose (1×10^8 pfu/dose) groups reported VRC-prompted injection-site AEs during the first 5 days post vaccination, compared with 14.3% of subjects in the placebo group. The most frequently reported injection-site AEs in each group were injection-site pain, followed by injection-site swelling, and injection-site erythema, with no evident dose dependency. The majority of injection-site AEs were mild to moderate in intensity, with a median duration of 1 to 3 days.

Systemic Adverse Events

The frequency of the following systemic AEs was reported in a higher proportion of vaccinated subjects compared with subjects who received placebo or were unvaccinated: headache, pyrexia, fatigue, myalgia, arthralgia, arthritis, chills, sweats (hyperhidrosis), nausea, abdominal pain, and rash. These systemic AEs were usually reported during the first 7 days post vaccination; the majority were of mild to moderate intensity and of short duration (less than 1 week).

In the V920-009 trial, solicited systemic AEs were reported for a higher proportion of subjects in the V920 (61.6%) group compared with subjects in the placebo group (43.3%) at any time point. The most frequently ($\geq 10\%$) reported systemic AEs in the V920 and placebo groups were headache, pyrexia, myalgia, and fatigue. Other solicited systemic AEs reported more commonly in the V920 group compared with the placebo group included nausea, arthralgia, and hyperhidrosis. The incidences of other systemic AEs including arthropathy, joint stiffness, and joint swelling were comparable between the V920 and placebo groups (Table 19).

In the V920-012 trial, solicited and unsolicited systemic (non-injection-site) AEs were reported for 62.3% of subjects in the Combined Lots group, 68.5% of subjects in the High Dose group, and 33.8% of subjects in the placebo group from Days 1 to 42. The most frequently ($\geq 10\%$) reported systemic AEs in the Combined Lots, High Dose, and placebo groups were pyrexia, headache, arthralgia, pain, and chills. Other systemic AEs reported more commonly in any V920 group compared with the placebo group included nausea, fatigue, influenza-like illness, and myalgia (Table 19). The majority of these AEs were mild to

moderate in intensity, with a median duration of 1 to 3 days. Arthritis was reported at a rate <5%, however this was at a higher frequency in the vaccinated subjects than placebo subjects and is discussed further below. The most frequently reported systemic AEs as assessed by the investigator as vaccine-related (>5% in one or more vaccination group) from Days 1 to 42 post vaccination were pyrexia, headache, arthralgia, chills, and fatigue. The majority of vaccine-related systemic AEs were mild or moderate in intensity, with a median duration of 1 day.

An additional systemic AE of abdominal pain was reported in a higher proportion of subjects in the Immediate Vaccination group (17.1% [including 1 severe event]) compared to the Deferred Vaccination control group (7.3%) in the V920-011 trial.

Table 19. Subjects With Solicited Systemic Adverse Events by System Organ Class in the V920-009 Trial (Incidence > 0%, Subjects with Week 1, Week 2, or Month 1 Visit)

	V920		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	498		499	
with one or more solicited systemic adverse events	307	(61.6)	216	(43.3)
with no solicited systemic adverse events	191	(38.4)	283	(56.7)
Gastrointestinal disorders	48	(9.6)	33	(6.6)
Mouth ulceration	13	(2.6)	13	(2.6)
Nausea	40	(8.0)	22	(4.4)
General disorders and administration site conditions	203	(40.8)	108	(21.6)
Fatigue	92	(18.5)	67	(13.4)
Pyrexia	171	(34.3)	74	(14.8)
Musculoskeletal and connective tissue disorders	171	(34.3)	120	(24.0)
Arthralgia	35	(7.0)	29	(5.8)
Arthropathy	3	(0.6)	1	(0.2)
Joint stiffness	2	(0.4)	1	(0.2)
Joint swelling	2	(0.4)	2	(0.4)
Myalgia	162	(32.5)	114	(22.8)
Nervous system disorders	184	(36.9)	116	(23.2)
Headache	184	(36.9)	116	(23.2)
Skin and subcutaneous tissue disorders	33	(6.6)	28	(5.6)
Hyperhidrosis	16	(3.2)	13	(2.6)
Rash	18	(3.6)	16	(3.2)
Vascular disorders	1	(0.2)	0	(0.0)
Haemorrhage	1	(0.2)	0	(0.0)
Every subject is counted a single time for each applicable row and column.				
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.				

Table 20. Subjects With Systemic Adverse Events in the V920-012 Trial (Incidence ≥ 5% in One or More Vaccination Groups, Day 1 to 42 post vaccination, All Subjects as Treated Population)

	V920 Combined Lots		V920 High Dose		Placebo	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	791		260		133	

with one or more systemic adverse events	493	(62.3)	178	(68.5)	45	(33.8)
with no systemic adverse events	298	(37.7)	82	(31.5)	88	(66.2)
Gastrointestinal disorders	93	(11.8)	33	(12.7)	8	(6.0)
Nausea	40	(5.1)	14	(5.4)	1	(0.8)
General disorders and administration site conditions	317	(40.1)	126	(48.5)	8	(6.0)
Chills	50	(6.3)	27	(10.4)	1	(0.8)
Fatigue	45	(5.7)	20	(7.7)	3	(2.3)
Influenza like illness	44	(5.6)	9	(3.5)	1	(0.8)
Pain	86	(10.9)	33	(12.7)	2	(1.5)
Pyrexia	168	(21.2)	76	(29.2)	1	(0.8)
Infections and infestations	59	(7.5)	20	(7.7)	12	(9.0)
Musculoskeletal and connective tissue disorders	225	(28.4)	89	(34.2)	9	(6.8)
Arthralgia	135	(17.1)	53	(20.4)	4	(3.0)
Myalgia	40	(5.1)	23	(8.8)	1	(0.8)
Nervous system disorders	193	(24.4)	81	(31.2)	19	(14.3)
Headache	167	(21.1)	67	(25.8)	15	(11.3)
Respiratory, thoracic and mediastinal disorders	48	(6.1)	15	(5.8)	7	(5.3)
Skin and subcutaneous tissue disorders	62	(7.8)	23	(8.8)	6	(4.5)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Lot A, B, C = 2×10^7 PFU; High Dose = 1×10^8 PFU

Subjects were solicited for events of joint pain, joint swelling, rash, and blisters on the Vaccination Report Card (VRC). The investigator then reviewed the totality of the symptoms and provided the adverse event terms provided in the table (e.g., arthritis, arthralgia).

The reference table of ADRs within the 4 Phase 2/3 studies has been amended by the key methodological differences in data collection methods, explaining much of the frequency variations among the different studies. This allows a good comparison to the frequency indications in the SmPC. It has been noted that the rash and chills frequency occurring in the V920-011 study is slightly higher than the SmPC indications, but this is acceptable, since this was an open-label study less considered by the applicant for AE frequency determination; rash is considered borderline (between common and very common) and chills an outlier compared to the other studies.

Table 21. Subjects with Injection-Site and Systemic Adverse Events in V920 Phase 2 and 3 Clinical Trials Conducted in African and Non-African regions

Adverse Event [†]	V920 Clinical Trial*			
	V920-009 (N=498) n (%)	V920-010 (N=5643) n (%)	V920-011 (N=217) n (%)	V920-012 (N=791) n (%)
Injection-site pain	152 (30.7) [‡]	362 (6.8)	166 (76.5)	554 (70.0)
Headache	184 (36.9)	1690 (33.5)	158 (72.8)	167 (21.1)
Pyrexia [§]	171 (34.3)	12 (0.2)	111 (51.2)	168 (21.2)
Fatigue	92 (18.5)	1301 (26.1)	110 (50.7)	45 (5.7)
Myalgia [§]	162 (32.5)	857 (17.3)	67 (30.9)	40 (5.1)
Arthralgia [§]	35 (7.0)	915 (18.5)	79 (36.4)	135 (17.1)
Arthritis	2 (0.4)	0	7 (3.2)	29 (3.7)
Nausea	40 (8.0)	27 (0.6)	12 (5.5)	40 (5.1)
Chills	5 (1.0)	83 (1.7)	40 (18.4)	50 (6.3)
Rash	18 (3.6)	0	25 (11.5)	18 (2.3)
Hyperhidrosis	16 (3.2)	17 (0.3)	2 (0.9)	4 (0.5)
Abdominal pain	7 (1.4)	47 (1.0)	37 (17.1)	6 (0.8)
Key Trial Design and Safety Assessment Methods				
V920-009				
<ul style="list-style-type: none"> • Double-blind, randomized, placebo-controlled trial • Subject memory aid not used • Assessed the absence or presence of solicited injection-site and systemic AEs at discrete time points (Week 1, Week 2, Month 1). • Subject temperatures were measured at study visits. 				
V920-010				
<ul style="list-style-type: none"> • Open-label, ring vaccination trial • Subject memory aid not used • Assessed the absence or presence of solicited injection-site and systemic AEs at discrete time points (Minute 30, Day 3, Day 14). • Subject temperatures were measured at study visits. • Subjects were provided antipyretics/analgesics after vaccination. 				

V920-011
<ul style="list-style-type: none"> • Open-label trial with immediate and deferred vaccination groups • Subject memory aid (ie, diary card) used to record solicited injection-site and systemic AEs in safety substudy Days 0 to 28 postvaccination. • Thermometers were provided to subjects for the measurement of daily temperatures postvaccination.
V920-012
<ul style="list-style-type: none"> • Double-blind, randomized, placebo-controlled trial • Subject memory aid (ie, VRC) used to record solicited injection-site AEs from Days 1 to 5 postvaccination and to record daily temperature measurements and solicited joint and skin events from Days 1 to 42 postvaccination. • Thermometers were provided to subjects for the measurement of daily temperatures postvaccination.
<p>* The subject populations are: All Subjects as Treated (ASaT), V920-009 trial: All Subjects Vaccinated, V920-010 trial: Immediate Vaccination group, Safety sub-study, V920-011 trial: ASaT, Combined V920 group, V920-012 trial.</p> <p>[†] The postvaccination time periods for the analysis of injection-site pain AEs are: Week 1, V920-009 trial; Day 3, V920-010 trial; Days 0 to 7, V920-011 trial; Days 1 to 5, V920-012 trial. The postvaccination time periods for the systemic AEs are: All time periods (Week 1, Week 2, and Month 1) for solicited systemic AEs and Day 1 to Year 1 for unsolicited AEs, V920-009 trial; All time periods (Day 0 to 14), V920-010 trial; Day 1 to 28, V920-011 trial; Day 1 to 42, V920-012 trial.</p> <p>[‡] The denominator of subjects was 495 for the safety analysis (and assessment of AEs of injection-site pain) at the Week 1 visit in the V920-009 trial.</p> <p>[§] Pyrexia was reported as fever in the V920-010 trial. Pyrexia was reported as feverishness, myalgia was reported as muscle pain, and arthralgia was reported as joint pain in the V920-011 trial</p> <p> Arthritis was reported as joint swelling in the V920-009 and V920-011 trials. The arthritis term reported in this analysis for the V920-012 trial is the composite term (see [Ref. 5.3.5.1: P012V01V920: 12.2.2.5.2]).</p>

Intrinsic factors including demographic characteristics of age, gender, and race were evaluated in the V920-012 trial. Regional differences were examined as extrinsic factors by evaluating solicited AEs in the V920 clinical trials (V920-009, -010, and -011) conducted in the African regions during the 2014-2016

epidemic and the V920-012 clinical trial that was conducted in non-African region. The safety profile of V920 was generally consistent across gender, age, race, and geographic region with the aforementioned higher risk of arthritis in females.

Serious adverse event/deaths/other significant events

Within the clinical development of Phase 1 studies, 14 subjects reported SAEs, and only one SAE resulted in death after a motor vehicle accident. All SAEs in the Phase 1 studies were not considered to be related to study vaccine. Regarding serious adverse events in general, data from all blinded, placebo-controlled clinical trials (V920-001 to -005 as well as -009 and -012) were integrated and compared with placebo. There was a low overall incidence of SAEs across all trials. In the integrated analysis of blinded trials, SAEs occurred in 3.4% of all vaccine recipients and 7.8% of placebo recipients through 1 year post vaccination. The constellation of SAEs in the blinded trials was consistent with conditions commonly observed in the trial population. Few SAEs were considered related to vaccination by investigators in the blinded studies. No V920 recipients discontinued due to SAEs.

In Phase 2/3 studies, regarding deaths, there was no striking incidence of events with a fatal outcome. Deaths were generally balanced among vaccine and placebo recipients. None of the deaths were considered vaccine-related by the investigators.

In the V920-009 trial, 11 subjects (1.1%) experienced an AE that resulted in death. Overall, the nature and type of fatal AEs reported in the V920 group are consistent with events anticipated in the population or a specific demographic, and do not suggest increased risk due to vaccination.

In the V920-012 trial, 3 subjects experienced 1 SAE each that resulted in death. The events included craniocerebral injury due to a fall, hepatic failure due to alcoholism, and road traffic accident. All of these events, due to extrinsic factors, do not indicate increased risk due to vaccine.

In the V920-010 trial, 18 (0.3%) adult vaccinated subjects experienced an SAE that resulted in death. EVD was the most frequently reported reason for death. It is important to note, however, that all cases of EVD reported for subjects randomized to the Immediate Vaccination group occurred in unvaccinated subjects or in vaccinated subjects prior to 10 days postvaccination. No subject who received study vaccine developed EVD 10 or more days following vaccination. None of the deaths in this trial was considered by the investigator to be related to the study vaccine.

In trial V920-011, 19 of 25 subjects (=0.2% of study population) who died had received V920. The proportions of subjects who died were comparable in each vaccination group with 8 deaths in the Immediate Vaccination group, 6 deaths (including a post-6-month postpartum haemorrhage) in the Deferred Vaccination group (prior to vaccination), and 11 deaths in the Deferred-Crossover group (after vaccination), all but one event occurred during the 6-months follow-up each. None of the SAEs and deaths was considered to be related to study vaccine by the investigator. One subject experienced an event of severe abdominal pain on Day 10 postvaccination and died from an unspecified aetiology 8 days later.

Regarding other Serious Adverse Events, in the integrated analysis of the blinded Phase 1/2/3 studies, the most commonly reported SAE from Days 1 to 365 for subjects in the V920 group was malaria (1.5% of subjects in the V920 group and 5.6% subjects in the placebo group); all of the SAEs of malaria were reported in the V920-009 trial. In addition to the V920-009 trial, SAEs of malaria were reported in the V920-010 trial in Guinea and V920-011 trial in Sierra Leone. In the V920-011 trial, more subjects in the Immediate Vaccination group reported SAEs of malaria than subjects in the Deferred Vaccination and Deferred-Crossover groups (12 subjects versus 2 subjects in the Deferred Vaccination group and 3 subjects in the Deferred-Crossover group). The basis for this difference is not clear. However, Sierra Leone has one of the highest rates of malaria in the world and the diagnosis is frequently made clinically rather than by laboratory confirmation. In the cases of malaria diagnosed without a conclusive diagnostic

laboratory test, it is unclear whether febrile reactions postvaccination may have been given the clinical diagnosis of malaria. In addition, the seasonality of malaria and the different seasons that subjects were vaccinated in the Immediate and Deferred-Crossover groups may partly account for the differences in numbers of cases among the groups.

Since the time of integration of the SAE data described above, SAE data from Months 6 to 24 post vaccination, the longest time period for SAEs collected to date in the V920 program, have become available for the V920-012 trial. Of the 65 total SAEs reported from Day 1 to Month 24 post vaccination, 39 SAEs were reported for 27 subjects from Month 6 to Month 24 post vaccination. Most of these SAEs were reported as single events by one subject each. Three SAEs with fatal outcome were reported from Day 1 to Month 24 post vaccination. None of the SAEs were considered related to study vaccine by the investigator. The integrated SAE data were not updated to include the additional SAE data from the V920-012 trial as only 7 subjects experienced SAEs from Months 6 to 12 post vaccination.

In the V920-010 trial, 80 subjects experienced SAEs, including 65 vaccinated subjects (61 adults and 4 children). The most common diagnosis was EVD in 39 (48.7%) of 80 subjects. One SAE of febrile reaction in one subject and one SAE of anaphylaxis in another subject, which resolved without sequelae, were judged by the investigator and Sponsor (the WHO) to be related to vaccination, and one SAE of influenza-like illness, which also recovered without sequelae, was considered possibly-related.

Evaluation of Arthritis Adverse Events

Joint-related AEs occurred more commonly in V920 recipients compared with placebo recipients across the V920 clinical program. Adverse events of arthralgia were reported for 10% to 50% of subjects, and arthritis was less commonly reported (<5% in most trials but up to 24% in the V920-005 trial). The majority of joint events were mild to moderate in intensity. Arthralgia was generally reported in the first few days following vaccination and resolved within one week after onset, whereas arthritis was generally reported within the first few weeks following vaccination and resolved within several days to weeks after onset. Some subjects experienced severe events or recurrent or prolonged joint symptoms lasting up to 2 years following vaccination, the longest follow-up to date. In a small number of subjects, vaccine virus was recovered from joint effusion samples as a possible hint for a virally mediated process. Arthralgia, as described for systemic AEs in the V920-012 trial, was very commonly observed in the first few days following vaccination, whereas arthritis was observed less commonly in most trials.

In the V920-009 trial, the verbatim term "arthritis" was not solicited and "arthritis" was not reported as an unsolicited AE. However, the terms arthropathy, joint stiffness, and joint swelling which align with the definitions of arthritis applied in the V920-004 and V920-005 trials were captured. Joint complaints other than arthralgia were reported for a few subjects in the V920-009 trial and the events were comparable in the V920 and placebo groups: arthropathy (3 subjects in the V920 group, 1 subject in the placebo group), joint stiffness (2 subjects in the V920 group, 1 subject in the placebo group), and joint swelling (2 subjects in the V920 group, 2 subjects in the placebo group).

In the V920-012 trial, arthritis was solicited based upon the early results from V920-005. The incidences of arthritis (composite term: including MedDRA preferred terms (PT) of arthritis, monoarthritis, polyarthritis, osteoarthritis, joint swelling, or joint effusion) from Days 5 to 42 were 3.7% and 3.1% for subjects in the Combined Lots and High Dose groups, respectively. No subjects in the placebo group experienced arthritis. The following MedDRA PT events constituted the composite arthritis events:

- Arthritis: 1.0% and 0.4% in the Combined Lots and High Dose groups, respectively
- Joint effusion: 0.4% in the High Dose group
- Joint swelling: 2.5% and 2.7% in the Combined Lots High Dose groups, respectively
- Osteoarthritis: 0.1% in the Combined Lots group

- Polyarthrititis: 0.1% in the Combined Lots group

In the V920-012 trial, a post-hoc multivariate logistic regression analysis that controlled for covariates demonstrated that female sex and a positive medical history of arthritis were independent baseline variables that are associated with a 2.2- to 2.8-higher risk of developing post vaccination arthritis, respectively, with 95% CI lower bounds of 1.1 and 1.3, respectively.

In contrast with other trials, arthritis was reported by a higher (23.5%) proportion of V920 recipients in the V920-P005 trial for reasons that have not been elucidated. Half of the subjects with arthritis among vaccinees reported Grade 3 severity of symptoms, and 6 subjects reported recurrent or persistent joint symptoms up to 2 years post vaccination.

Evaluation of Skin and Mucosal Adverse Events

In the V920 clinical program, certain skin- and mucosal-related AEs were observed in subjects following vaccination. These events generally occurred at a low incidence, were mild to moderate in intensity, and were self-limited. Across the V920 program, vesicular lesions of the skin (blisters) appearing in the first few weeks after vaccination were reported in some of subjects. In addition, some subjects vaccinated with V920 experienced oral ulcers. A small number of rashes including vesicular lesions of the skin were positive for V920 vaccine virus by RT-PCR testing, suggesting that both post vaccination rash and vesicles may be virally mediated. The assessment of vaccine virus in oral ulcers by RT-PCR was not conducted.

The majority of data for the analyses of skin and mucosal events for the Phase 1 clinical program are from the V920-004 and V920-005 trials, as these trials have the most comprehensive and representative data pertaining to these events.

In the V920-004 analysis, a comprehensive analysis of temporally-associated post-vaccination dermatitis was performed; this term was defined as a solicited AE preferred term of mucosal lesions or skin lesions, or unsolicited AE preferred term of dermatitis, petechiae, rash (including generalized, macular, papular, or vesicular rash), skin lesion, skin mass, or skin ulcer with onset within 56 days of vaccination; however, symptoms of dermatitis were captured differently across cohorts. In the V920-005 trial, skin- and mucosal-related AEs were defined by the solicited term of skin lesions and unsolicited terms of rash (including erythematous, generalized, macular, maculo-papular, papular, and vesicular rash), mouth ulceration, papule, and cutaneous vasculitis.

In addition to the V920-004 and V920-005 analyses, a comprehensive analysis for rash AEs was presented for the V920-012 trial. In order to capture all possible cases of rash in the V920 012 trial, the following preferred terms were defined before database lock based on review of blinded safety data and included in the composite term for rash: petechiae, purpura, rash, rash generalized, rash macular, rash papular and rash vesicular.

In the V920-009 trial, rash was a solicited AE, and was reported in 3.6% of V920 recipients and 3.2% of placebo recipients. Mouth ulceration was reported for 2.6% of subjects in both the V920 and placebo groups.

In the V920-012 trial, rash and vesicular lesions were solicited AEs. The proportions of subjects with rash (composite term: MedDRA PT petechiae, purpura, rash, rash generalized, rash macular, rash papular, and rash vesicular) from Days 1 to 42 post vaccination were low – for the Combined Lots (3.8%), High Dose (3.8%), and placebo (1.5%) groups. The proportions of subjects with vesicular lesions from Days 1 to 42 post vaccination similarly were low – for the Combined Lots (1.5%), High Dose (1.5%), and placebo (0.0%) groups. An assessment algorithm for subjects who reported AEs of rash and vesicular lesions involved referrals to a dermatologist for skin events and/or biopsy/fluid sampling to identify V920 via RT-PCR, if feasible. However in this trial, of 6 subjects with skin AEs, RT-PCR results identified V920 from

a biopsy in only 1 subject with an AE of dermatitis. RT-PCR results were positive for V920 in the vesicular fluid of 1 subject with blisters tested.

In the V920-005 trial, there is a heterogeneous picture regarding rash and vesical events in vaccinated and placebo subjects: 29.4% of all V920 recipients and 30.8% of placebo subjects experienced skin- and mucosal-related AEs. The most frequently reported skin- and mucosal-related AE was mouth ulceration, with 15.7% of subjects in the V920 group compared with 23.1% of subjects in the placebo group. Rash was reported for 4.9% of V920 recipients and 7.7% of placebo recipients. Two subjects experienced AEs assessed by the investigator to be cutaneous vasculitis. Review of clinical and histologic evidence in each case of reported cutaneous vasculitis by external experts determined that a systemic vasculitis process is not favoured. In both cases, the evidence suggested hypersensitivity reaction, and in one, post-viral exanthem.

Hypersensitivity Events

Only one subject had an SAE of anaphylaxis, in the V920-010 trial, that was considered to be vaccine-related by the investigator and trial Sponsor. This subject developed generalized pruritus, urticaria, and oedema of the face and lips approximately 12 hours after vaccination. The subject presented the following day, was treated with steroids, and improved without hospitalization.

Overdose

There were no reports of overdose in the V920 trials. All V920 trials administered a single dose of V920, except for the V920 002 trial in which 2 doses were administered. The majority of subjects enrolled in the V920 trials received a single dose with the exception of 6 subjects in the V920-011 trial who were unintentionally vaccinated twice after attempting to enrol multiple times at several trial locations. The median time between vaccinations was 48 days (range: 27 to 98 days). All 6 subjects were followed for 6 months following the second dose of V920 and no vaccine-related SAEs were reported.

Laboratory findings

Laboratory assessments were routinely collected in the Phase 1 and the V920-009 trials. Decreases in white blood cell (WBC), lymphocyte, and neutrophil count were reported in a higher proportion of V920 recipients compared with placebo recipients. Decreases in white blood cell, lymphocyte, and neutrophil count were reported commonly after vaccination with a viral vaccine.

The events were transient, occurring a few days following vaccinations and were in toxicity grades 1-2. There were no associated infections reported for subjects who experienced AEs associated with hematologic abnormalities, and these events were not considered clinically significant, although theoretically can be associated with a higher risk of infection during the period of depletion.

In the V920-012 trial, a total of 72 subjects who experienced arthritis, arthralgia, or rash had occasional laboratory testing conducted. Mild elevations of C-reactive protein (CRP) were noted in 17 out of 54 subjects. Mild to moderate elevations of ALT were also noted in 6 subjects out of 39 subjects who had additional CRP testing, both hinting to a mild inflammatory sign.

Vaccine Viremia and Viral Shedding

Vaccine viremia evaluation and viral shedding was investigated in the context of the ERA. V920 vaccine is a live, attenuated vaccine that is replication competent. Shedding of V920 has been observed in urine and saliva of <10% adult subjects and identified in vesicles. Transmission of V920 through close personal contact is considered as a theoretical possibility.

In the Phase 1 clinical program, subjects in the blinded and open-label trials were assessed for vaccine viremia (detection of the V920 in the blood) and viral shedding of V920 post-vaccination using real-time

reverse transcriptase-polymerase chain reaction (RT-PCR) assays. The time points for PCR testing varied by trial. The assay methodology is described in the efficacy section.

The qualitative results (positive or negative for vaccine viremia) were presented for subjects who received 2×10^7 pfu/dose V920 or higher for the Phase 1 trials, with the limitation that the sensitivities of the assays for detection of vaccine viremia are different and cannot be compared. The RT-PCR assay methods were not standardized across the trials and used different qualitative and quantitative definitions for detection of vaccine viremia.

All subjects who received 2×10^7 pfu/dose of V920 or higher in the V920-001, V920-002, and V920-005 trials had detectable vaccine viremia at some time point following vaccination. The proportions of subjects with vaccine viremia decreased over time, and all vaccine viremia resolved by Day 14 post-vaccination in the V920-001 and V920-005 trials. For the V920-002 trial, 3 subjects (30.0%) each in the 2×10^7 pfu/dose and 1×10^8 pfu/dose V920 groups still had detectable vaccine viremia at Day 7 post-vaccination, with no other time points tested in this trial. The V920-004 trial had the highest number of subjects ($n = 408$) tested for vaccine viremia, and of these subjects, 80 (20%) had detectable viremia at 1 or more time points following vaccination. In this trial, a similar number of subjects had RT-PCR testing performed in both the 2×10^7 pfu/dose and 1×10^8 pfu/dose V920 groups, but a higher proportion of subjects (62.2%) who received the 1×10^8 pfu/dose V920 had vaccine viremia compared with subjects (21.7%) who received the 2×10^7 pfu dose. In 2×10^7 pfu/dose and 1×10^8 pfu/dose V920 groups, the incidence of viremia peaked on Days 1 and 2 post-vaccination respectively; all vaccine viremia for subjects in these V920 dose groups resolved by Day 28 post-vaccination.

In the V920 Phase 1 open-label trials, all adult subjects in the 2×10^7 pfu/dose V920 group of the Phase 1 open-label trials had detectable vaccine viremia at some time. On Day 1, the proportions of subjects with vaccine viremia were 90.0%, 100.0%, and 86.7% in the V920-006, V920-007, and V920-008 trials, respectively. By Day 3 post-vaccination in the V920-006 and V920-008 trials, all subjects had detectable vaccine viremia. The proportions of subjects in the 2×10^7 pfu/dose V920 group with vaccine viremia decreased over time; all cases of subjects in this group resolved by Day 6 and Day 7 post-vaccination in the V920-006 and V920-008 trials. For the V920-007 trial, 3 adult subjects (18.8%) in the 2×10^7 pfu/dose V920 group still had detectable vaccine viremia at Day 7 post-vaccination, with no later time points tested in this trial.

In summary, vaccine viremia was commonly observed among adults vaccinated with V920, but generally resolved by Day 14 post-vaccination. The V920 Phase 2 and 3 trials did not assess vaccine viremia and viral shedding.

Viral shedding (identification of the V920 virus in saliva and urine) was seen in a few adult subjects at low copy number. Shedding might also possibly occur via other body fluids than saliva or urine, such as semen, sweat, vesicular liquid, breastmilk, aerosol, vomit. In trial V920-012, RT-PCR evaluation on vesicular lesions for 2 subjects was negative, and on blisters for 1 subject was positive (687,160 copies/mL). A viral shedding assessment was not performed for all subjects in the V920-005 trial. Per protocol, the shedding assessment was stopped after the first 10 subjects because all results were negative. Although transmission of the virus through close personal contact is a theoretical possibility, it is considered low risk, because of the low magnitude of shedding observed.

Secondary transmission of V920 was not evaluated in the V920 program.

Safety in paediatric population

In the V920-007 trial, 20 school-age children and 20 adolescents were enrolled and vaccinated. Two adolescents (5.0%) withdrew early from the trial; one of the adolescents withdrew consent within 14 days

following vaccination. The mean age of school-age children was 9.2 years (range: 7 to 11 years) and of adolescents was 14.7 years (range: 13 to 17 years).

In the first 14 days following vaccination, solicited local AEs were reported in 7 school-age children (35%) and in 5 adolescents (25%); these incidence rates were comparable to those in adult subjects who received 2×10^7 pfu (9 subjects, 56%). Solicited systemic AEs were reported in 17 school-age children (85%) and in 19 adolescents (95%); in comparison, solicited systemic AEs were reported in 13 (81%) adult subjects who received 2×10^7 pfu.

The majority of the solicited local TEAEs had an early onset, i.e. in the first day following vaccination, and all solicited TEAEs were assessed as Grade 1 or Grade 2 in severity.

Most solicited local and systemic AEs abated within 3 days (median duration ≤ 3 days), but the median duration for decreased appetite was 4.5 days. One school-age child had diarrhoea for 6 days, and 1 adolescent had injection site swelling that lasted 9 days. Arthralgia was the only solicited TEAE that lasted ≥ 14 days, with a maximum duration of 16 days in 1 adolescent.

In the non-randomized arm of the V920-010 ring vaccination trial, there have also 194 children between 6 - 17 years been included. Regarding included children in the non-randomized arm, overall, 38.2% of 194 vaccinated children reported a solicited AE from Days 0 to 14 following vaccination. Solicited injection-site pain was reported for 5% of these subjects. The most commonly reported solicited systemic AEs were headache, fatigue, muscle pain, myalgia, and arthralgia. Most of the solicited AEs reported for children were mild in intensity.

Two children had temperatures $\geq 38^\circ\text{C}$, and AEs of fever were reported accordingly; however, the intensity of these events was not assessed.

Overall, the median duration of solicited AEs with any intensity (mild, moderate, severe) reported for children was 2 days (IQR: 1 to 3 days). Only one child reported a severe AE of fatigue, which had a duration of 4 days.

An amendment to Expanded Access Protocol 5 (EAP5; a compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo) to include pregnant women (after the first trimester) and infants ≥ 6 months was approved in June 2019, and vaccinations in these populations began on 13 June 2019. Under this protocol amendment, vaccinated pregnant women and children (6 to 11 months of age) will be actively monitored for AEs by the trial sponsor through 21 days post-vaccination. Vaccinated pregnant women will also be followed until the end of pregnancy to assess the clinical status of the newborn. Once the outbreak has concluded and the database for EAP5 is cleaned and locked, an analysis of the impact of V920 in this outbreak will be prepared, which will include an evaluation of safety and efficacy. The Applicant is requested to share the safety data once the trial is completed and all data has been made available by the sponsor conducting EAP5 (the WHO and DRC Ministry of Health). As the EAP is being conducted during an active and ongoing outbreak, completion dates cannot be predicted at this time.

Laboratory findings

In school-age children and adolescents, mean changes from baseline to the end of trial in ALT, AST, and creatinine were small and remained within normal ranges for most subjects for the duration of the trial. Shifts in toxicity grade for these serum chemistry parameters were from Grade 0 at baseline to Grade 1 or 2 post vaccination.

Serious Adverse Events in Children

One school-aged child and 1 adolescent experienced Grade 2 malaria during the trial; these SAEs were considered by the investigator not to be related to vaccination.

Viremia and shedding

Vaccine viremia and shedding were more pronounced in school-age children and adolescents vs. adults. All school-age children and adolescents were viraemic on Day 1. At Day 7, V920 RNA was detectable in saliva in 7 school-age children (35%) and in 14 adolescents (88%), and in a urine sample from 1 school-age child (11%). The shedding in saliva did not correlate with an increased incidence of oral symptoms.

Overall results

V920-007 was the first trial, which evaluated safety in school-children and adolescents. Vaccination with V920 was tolerated well in both age groups with comparable AE reporting and the incidences of solicited symptoms were comparable to the frequencies adults reported in the Phase I trials. The most frequently reported solicited local AE across school-age children and adolescents was injection site pain and the most frequently reported systemic AEs included headache, fatigue, and pyrexia. Arthralgia was reported by 18 % of subjects and one adolescent reported with 16 days duration. Shedding in saliva and urine up to 7 days were reported only in children that long.

Safety in Special Populations

Use in Pregnancy and Lactation

Pregnant and breastfeeding women were excluded from V920 trials; however, several women were incidentally found to be pregnant after vaccination and the pregnancy outcomes were reported. Among the trials with available data, the majority of pregnancies occurred in the V920-011 trial. Pregnancies reported with onset within 2 months after enrolment or vaccinations were followed to resolution. A total of 261 pregnancies were reported during the trial. Of these pregnancies, 107 pregnancies were reported as occurring within 2 months after enrolment or vaccination: 58 resulted in live births (55 full term and 3 pre-term), 30 early pregnancy losses, and 9 still births ≥ 20 weeks of gestation.

Regarding early pregnancy losses, their rate has been shown 3-fold higher in the V920 vaccinees compared to the deferred control group. Data are not sufficient to draw any conclusion at this stage. Lack of reliable data on background rates of pregnancy and neonatal outcomes in the affected regions also makes a contextual assessment of the data challenging.

No data is available for subjects who were breastfeeding in the V920 clinical program.

Immunocompromised subjects

The safety of V920 has not been assessed in severely immunocompromised individuals. In individuals with a defect in innate or adaptive immunity, the live-replicating vaccine could theoretically produce a more active or long-lasting infection with the vaccine virus than normal, the outcome of which could be a severe illness. It is not known what effects V920 may have on individuals with the following conditions:

- Severe humoral or cellular (primary or acquired) immunodeficiency, e.g., severe combined immunodeficiency, agammaglobulinemia and AIDS or symptomatic HIV infection. A CD4+ T-lymphocyte count threshold for use in asymptomatic HIV-positive individuals has not been established.
- Current immunosuppressive therapy, including high doses of corticosteroids. This does not include individuals who are receiving topical or low-dose parenteral corticosteroids (e.g., for asthma prophylaxis or replacement therapy).
- Blood dyscrasias, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the hematopoietic and lymphatic systems.

- Family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Immunocompromised individuals may also not respond as well as immunocompetent individuals to V920 and could be more likely to develop EVD than immunocompetent individuals in case of exposure to Zaire Ebola virus despite appropriate vaccine administration.

Safety related to drug-drug interactions and other interactions

No interaction studies have been conducted. As there are no data on co-administration of Ervebo with other vaccines, the concomitant use of Ervebo with other vaccines is not recommended and an interval of at least 4 weeks should be respected between the 2 administrations of live-virus vaccines.

Discontinuation due to adverse events

None of the discontinuations due to an AE or death were considered to be related to study vaccine by the investigator.

Post marketing experience

V920 is not currently authorised or marketed in any country.

2.6.1. Discussion on clinical safety

Phase I trials

Eight Phase 1 trials were conducted (V920-001, -002, -003, -004, -005, -06, -007, and -008) in the US and Canada, Europe (Switzerland and Germany), and regions of Africa not affected by the outbreak (Gabon and Kenya). The Phase 1 program included 795 adult subjects who received V920 as a single dose ranging from 3×10^3 pfu/dose to 1×10^8 pfu/dose, whereas 197 adult subjects who received a single dose of 2×10^7 pfu or higher of V920. 30 subjects received dosages 3×10^6 pfu, 1×10^7 pfu, or 1×10^8 pfu compared to placebo twice. 135 subjects received placebo in the Phase 1 blinded trials.

The incidence of reported solicited AEs was higher in the V920 dose groups compared to placebo. Solicited local AEs were reported more frequently with increasing dosages. After the second dosage, less AEs were reported compared to the first administration. Unsolicited AEs associated with laboratory abnormalities were more often reported from subjects vaccinated with V920 compared to placebo.

Within the blinded Phase I trials a heterogeneous reporting rate of 15% to 50% for arthralgia was observed. Reporting of arthralgia was not dosage dependent but occurred more frequently in V920 recipients as compared to placebo recipients. Because of this reporting the event of arthralgia should be followed up in the PSUR.

Myalgia, objective fever, and subjective fever were reported with a higher incidence in the V920 groups compared to placebo groups but showing no clear dose-dependent trend.

Solicited injection-site AE was most commonly reported in all Phase I trials. Solicited and unsolicited AE were mostly considered as Grade 1 or Grade 2 and were abated within 3 days.

The majority of data for the analyses of skin and mucosal events for the Phase 1 clinical program are from the V920-004 and V920-005 trials, as these trials have the most comprehensive and representative data pertaining to these events.

Rash was characterized in a variety of ways including generalized rash (2.3%), vesicular rash (0.5%), dermatitis (0.3%), or cutaneous vasculitis (0.01%) in clinical trials. In 6 out of 18 subjects tested, V920

virus was detected in rashes (described as dermatitis, vesicles or cutaneous vasculitis lesions) suggesting a virally mediated process post-vaccination.

Vaccine viremia (based upon RNA detection) was commonly observed among adults vaccinated in the Phase 1 trials but generally resolved by Day 14 post-vaccination. The V920 Phase 2 and 3 trials did not assess vaccine viremia and viral shedding. Viremia was more often detected after administration of both higher dose groups, i.e. 2×10^7 pfu and 1×10^8 pfu compared to 3×10^6 pfu and in children compared to adults. It appears to be less common after Day 3 post-vaccination and is rarely found at 7 or 14 days.

Shedding of V920 has been observed in urine and saliva at low incidence and low copy number in adult subjects (<1000 copies/mL) and identified in vesicles in 4 out of 10 adult patients. Viral shedding was of higher magnitude and more frequent in children and adolescents compared to adults. Transmission risk is considered very low. This theoretical safety concern has been adequately addressed in the section 4.4 of the SmPC. As a precaution, subject should avoid close association with and exposure of high-risk individuals to blood and bodily fluids for up to 6 weeks following vaccination. Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal.

Transient decreases in counts of lymphocytes, neutrophils and total white blood cells have also been observed, but no increased risk of infection has been reported. Those events could be theoretically associated to a higher risk of infection during the period of depletion. The mechanism leading to this variation in the white blood count is poorly understood. The Applicant is requested to follow up in PSURs on any additional data will be collected from completed and ongoing trials to document and/or explain the transient decreases in counts of lymphocytes, neutrophils and total white blood cells after vaccination and their repercussions for the safety of vaccinees.

V920-007 was the first trial to evaluate safety in 20 schoolchildren and 20 adolescents. Vaccination with V920 was tolerated well in both age groups with comparable AE reporting and the incidences of solicited symptoms were comparable to the frequencies reported by adults in the Phase I trials.

Phase 2/3 clinical trials

The total number of adult subjects vaccinated with V920 in double-blind, placebo-controlled trials was 2,171 and in open label trials was 13,826. A total of 15,398 subjects received the $\geq 2 \times 10^7$ pfu dose and 15,050 participants had the exact dose of 2×10^7 pfu; the blinded placebo-controlled studies incorporated 1,712 vaccinated with $\geq 2 \times 10^7$ pfu. Of these, 1,397 adults had the intended dose of 2×10^7 pfu. The phase 2/3 placebo-controlled randomized trials (Protocol 009 and Protocol 012) included 498 African subjects of Liberia and 1,061 subjects in US, Spain and Canada.

The frequencies listed in the SmPC are based on the higher frequency reported in either of the Phase 2/3 placebo-controlled randomized trials, Protocol 009 and Protocol 012.

The most commonly reported solicited systemic AEs in all the Phase 2 and 3 trials were headache, pyrexia, fatigue, myalgia, and arthralgia and these types of AEs were also consistent with those commonly reported (≥ 4 subjects in one or more vaccination groups) in the V920-012 trial, which was conducted in North-America and Europe. The increased frequency of the reports of headache, pyrexia, fatigue, and myalgia in the V920-009 trial compared with the V920-012 trial may be explained by the events being solicited in the former trial only. Arthralgia (or joint pain), which was solicited in both trials, was more frequently reported in V920-012 than V920-009. The extremely low report of pyrexia in the V920-010 trial is likely confounded by the provision of antipyretics to the subjects in this trial. Subjects were provided acetaminophen or ibuprofen at the time of vaccination. The increased frequency of reporting of all the solicited AEs in the V920-011 trial may be due to the open-label nature of the trial (compared with V920-009 and V920-012), and perhaps increased reporting of these events among subjects who were not affected by the Ebola outbreak compared with subjects in V920-010. The V920-011 trial also provided a diary card to subjects for the recording of post-vaccination events.

The V920 trials were designed and conducted by various sponsors, which led to heterogeneous study designs that did not prove conducive for integrating AE data. As a result of the differences, the AE datasets could not be properly harmonized and integrated to provide a meaningful and interpretable integrated dataset, which is acceptable given the context. An assessment of AEs or SAEs from the double-blind trials versus the open-label trials is not meaningful because the study vaccine that the subject received in the open-label trials was known by all and therefore, the assessment of AEs and SAEs in the open-label trials lacks objectivity due to reporting bias. Therefore, to preserve the integrity of the SAE analysis for V920 administered at the 2×10^7 pfu dose, only the SAEs from the double-blind trials were integrated. For a comprehensive evaluation of SAEs in the V920 clinical program, SAEs from all trials, including the open-label trials, were also summarized and the results are clinically meaningful without data integration.

Arthritis is an AE of special interest and therefore, events of arthritis were assessed in all Phase 2 and 3 clinical trials. The proportions of subjects who reported arthritis in the V920-009 and V920-010 trials were very low (only 2 subjects [0.4%] in V920-009 and none in V920-010). As noted, arthritis was not solicited in the V920-010 trial, and only a subset of subjects (201) were interviewed regarding joint symptoms at Week 2 post-vaccination in the V920-009 trial. Both factors may have impacted the reporting of arthritis AEs. In the V920-011 and V920-012 trials, in which arthritis was a solicited systemic AE, the proportions of subjects who reported this event were comparable (3.2% and 3.7%, respectively). Oligo-arthritis and rash appearing in the second week occur at a low incidence and are most of the times mild-moderate in severity and self-limited. Less than 5% of subjects in most trials (including pivotal Phase 3 safety study 012 with specific surveillance for joint and skin adverse events) experienced arthritis and/or rash, which in some cases may be vesicular or purpuric. In some cases, viral RNA has been identified by immunohistochemistry and/or RT-PCR in the joints or skin/vesicles. In one Phase 1 study the incidence of oligoarthritis was as high as 22%. The reason for this difference is not well understood. In an open label safety study in Sierra Leone (011-STRIVE), 17% complained of joint pains in the interval 5-28 days after vaccination. The arthritis and skin events appear to reflect direct viral injury and inflammation and do not have an immunopathological basis which could suggest an autoimmune disease. A subset of subjects in 005 and 012 continued to have persistent joint symptoms at the completion of the study (follow-up was up to 2 years). The 005 also reported several subjects with recurrent joint events following initial resolution of the events. This current study did not specifically analyse recurrences of joint events.

The risk of shedding via fluids in vesicles is considered very low in healthy people in line with the results from phase I studies but has not been investigated in immunocompromised patients. The risk of shedding via saliva or urine is considered low. Transmission of V920 through close personal contact is accepted as a theoretical possibility. As a precaution, vaccine recipients should avoid close contact with and exposure of high-risk individuals to blood and bodily fluids for at least 6 weeks following vaccination. High-risk individuals include:

- Immunocompromised individuals and individuals receiving immunosuppressive therapy (see section above),
- Pregnant or breast-feeding women (see section 4.6),
- Children <1 year of age.

Individuals who develop vesicular rash after receiving the vaccine should cover the vesicles until they heal to minimize the risk of possible transmission of V920 through open vesicles. For the same reason, individuals administered V920 should not donate blood for at least 6 weeks post-vaccination.

As there are no data on co-administration of V920 with other vaccines, the concomitant use of V920 with other vaccines is not recommended.

Non-intramuscular administration errors can lead to adverse events and delayed absorption in general as the subcutaneous space is less vascular. Administration of V920 is intended for intramuscular administration; there is no data on subcutaneous administration and subcutaneous administration is not recommended.

There is currently limited evidence related to the safety of V920 during pregnancy in humans. Pregnant women were excluded from clinical trials. However, a total of 261 women were incidentally found to be pregnant after vaccination. Although administration of V920 (5.28×10^7 pfu/animal) showed no effect in rats studies on mating, fertility, or foetal development following either single or multiple doses, the risk of adverse effects from administering the live virus vaccine to pregnant women remains unknown given the limited amount of clinical data available. Lack of reliable data on background rates of pregnancy and neonatal outcomes in the affected regions also makes a contextual assessment of the data challenging. However, more data will be available post-authorisation from the ring vaccination trial that is ongoing in DRC at the moment.

Severely immunocompromised subjects were excluded from V920 clinical trials. The largest number of HIV-positive individuals (with unknown immune compromise status) were enrolled in the V920-009 trial and exposed to V920. These subjects had a consistent safety profile compared with HIV-negative individuals, although the small numbers limit the conclusions that may be drawn.

The following safety topics should be considered as risk of the product to be discussed in the PSUR:

- *Arthritis*: The frequency of arthritis in vaccinees may vary according to factors such as gender, age, and personal and/or family history of this condition. The frequency of long-lasting arthritis after vaccination is poorly known as well as the frequency of disabilities associated with the condition. New data related to arthritis should be discussed through the PSURs.
- '*Hypersensitivity (including anaphylaxis)*' is considered a rare but severe adverse reaction following vaccination.
- '*Risk of infection due to transient decreases in counts of lymphocytes, neutrophils and total white blood cells*': those are theoretically associated to a higher risk of infection during the period of depletion. The mechanism leading to this variation in the white blood count is poorly understood. Based on a limited number of observations, no increased incidence of infectious episodes was observed after vaccination. Yet, more evidence is required to fully characterise the risk.
- *Behavioural changes regarding usage of other preventative Ebola preventative measures*: This concern is addressed in the SmPC and PL, section 4.4. However, any indication of preventable exposure should be explored when reviewing breakthrough cases. Any relevant publication should be discussed.
- *Safety and reduced efficacy in immunocompromised hosts*: Information is missing for this group which was not part of the clinical development plan.
- *Cases of Post-exposure prophylaxis (PEP)*: Given the nature of the vaccine and the contexts of its use, it is likely that the vaccine will be used in PEP. The knowledge on the use of the vaccine in PEP is very limited and any new data should be discussed in the PSURs.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Assessment of paediatric data on clinical safety

Two trials in the V920 clinical program, V920-007 and V920-010, enrolled and vaccinated 234 paediatric subjects 6 to <18 years of age. Based on the limited safety database the safety profile of V920 was similar

for children-adolescents 6 to 17 years of age compared to adults except for vaccine viremia and viral shedding, which were higher in children.

2.6.2. Conclusions on the clinical safety

The safety of Ervebo was assessed based on data collected in 15,398 healthy adults receiving $\geq 2 \times 10^7$ pfu in 8 phase 1 studies and 4 phase 2/3 studies. The chosen dosage of 2×10^7 pfu V920 was well tolerated by the enrolled subjects. The trials were not designed or conducted by the various sponsors with the final objective of data integration among them. The datasets could not be properly harmonized and integrated to provide a meaningful and interpretable integrated dataset. The integrated safety database consists of only serious adverse events (SAEs) data from 7 double-blinded studies (Phase 1 studies V920-001, V920-002, V920-003, V920-004, V920-005 phase 2/3 studies, V920-009, and V920-012). SAEs data across the randomized blinded trials were more uniformly collected and thus data integration was feasible.

A review of disposition and demographic data for subjects who received V920 at a dose of 2×10^7 pfu or higher demonstrated a comparable profile from all V920 doses combined except for the AESIs discussed (e.g. arthritis and rash).

The most common injection-site adverse reactions were injection-site pain (70.3%), swelling (16.7%) and erythema (13.7%). The most common systemic adverse reactions reported following vaccination with Ervebo were headache (36.9%), pyrexia (34.3%), myalgia (32.5%), fatigue (18.5%), arthralgia (17.1%), nausea (8.0%), chills (6.3%), arthritis (3.7%), rash (3.6%), hyperhidrosis (3.2%), and abdominal pain (1.4%). In general, these reactions were reported within 7 days after vaccination, were mild to moderate in intensity, and had short duration (less than 1 week). Arthralgia was generally reported in the first few days following vaccination, was mild to moderate in intensity, and resolved within one week after onset.

In 2015, a safety signal was reported in a phase 1 study regarding AEs Arthritis and joint problems and skin rashes. Arthritis (arthritis, joint effusion, joint swelling, osteoarthritis, monoarthritis or polyarthritis) was generally reported within the first few weeks following vaccination. Occurrence of Arthritis in V920-005 was 24/102 (23.5%: Very common) as compared to V920-012 results of 29/791 (3.7%: Common). The majority of arthritis reactions were mild to moderate and generally resolved within several days to weeks after onset. Few subjects experienced severe reactions or recurrent or prolonged joint symptoms lasting up to 2 years following vaccination, the longest follow-up period. In a small number of subjects, the vaccine virus was recovered from joint effusion samples, suggestive of a virally mediated process post-vaccination. The results of phase 3 study V920-012 show that female sex and a positive medical history of arthritis have statistically significant associations in multivariate analyses of composite arthritis terms with a 2.2- to 2.8-fold higher risk of post-vaccination arthritis and 95% confidence interval (CI) lower bounds of 1.1 and 1.3, respectively.

Rash was characterized in a variety of ways including generalized rash, dermatitis, vesicular rash or cutaneous vasculitis. In a small number of subjects, the vaccine virus was detected in rashes (described as dermatitis, vesicles or cutaneous vasculitis lesions) suggesting a virally mediated process post-vaccination. There was no evidence of systemic vasculitis.

In the Clinical Development Plan, the safety of Ervebo has not been established in pregnant or breastfeeding women, in newborns, in immunocompromised patients and in HIV+ patients.

A total of 261 women were incidentally found to be pregnant after vaccination but this data is too limited to be able to draw clinically meaningful conclusions. Even though animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, as a precautionary measure, it is preferable to avoid the use of Ervebo during pregnancy and pregnancy should be avoided for 2 months following

vaccination. Nevertheless, considering the severity of EVD, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

It is unknown whether Ervebo is secreted in human milk. A risk to the newborns/infants from breast-feeding by vaccinated mothers cannot be excluded.

A total of 234 children and adolescents 6 to <18 years of age were enrolled and received the clinical dose, showing a similar tolerability profile as adults.

536 (8.4%) of eligible, consented subjects were ≥65 years of age in the V920-010 trial, making the safety dataset in this population limited. Although it is not expected that the safety will differ in subject >65 years of age compared to younger subjects, as a precaution this limitation of the trials has been reflected as a warning in the SmPC.

The following safety topics should be followed up in post-marketing setting and reported in the PSUR:

- Risk of infection due to transient decreases in counts of lymphocytes, neutrophils and total white blood cells.
- Arthritis
- Safety and reduced efficacy in immunocompromised hosts
- Hypersensitivity (including anaphylaxis)
- Behavioural changes regarding usage of other Ebola preventive measures
- Cases of Post-Exposure Prophylaxis (PEP)

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA:

- HIV-infected individuals will be further evaluated in study V920-015 (ACHIV);
- vaccine viremia and shedding will be further evaluated in different trials post-authorisation (study V920-015 (ACHIV), study V920-016 (PREVAC));
- safety in pregnant and lactating women will be further evaluated in the ongoing Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of Congo.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	<ul style="list-style-type: none"> • Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts
Missing information	<ul style="list-style-type: none"> • Exposure during pregnancy • Exposure during lactation • Exposure in HIV-infected individuals

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
V920-015 ACHIV Ongoing	1) To evaluate the safety and tolerability of V920 in HIV-infected adults and adolescents. 2) To evaluate the immunogenicity of V920 via ZEBOV-specific antibody responses induced by V920 in HIV-infected adults and adolescents.	-Exposure in HIV-infected individuals -Viral shedding	Final report (Clinical Study Report)	30-Apr-2023
V920-016 PREVAC Ongoing	To evaluate the safety and immunogenicity of three vaccine strategies in adults and in children.	-Viral shedding	Final report (Clinical Study Report)	30-Apr-2021
V920-EAP5 Amendment #1 Ongoing	<u>Primary Objectives:</u> 1)To evaluate the safety of the V920 vaccine by following SAEs for 21 days for all participants. <u>Secondary Objectives:</u> 1)To summarize the cumulative incidence of EVD laboratory-confirmed cases amongst eligible persons after 21 days of monitoring, where a ring vaccination or geographically targeted vaccination strategy has been used. 2)To document the safety of a single dose of V920 vaccine in evaluating the solicited AEs (fever, headaches, tiredness, diarrhoea, vomiting, myalgia, arthralgia and local reactogenicity) for 21 days and the unsolicited AEs during the 21 days of follow-up for all participants.	-Exposure in pregnancy -Exposure in lactation	Final report	<i>Target: 2 years following official declaration of the end of the EVD outbreak in the DRC</i>

Risk minimisation measures

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Viral shedding/secondary transmission to close contacts, particularly immunocompromised hosts	Special warnings and precautions for use section of the product information. <i>What you need to know before you receive ERVEBO</i> section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: Viral shedding: V920-015 African Canadian Study of HIV-Infected Adults and a Vaccine for Ebola (ACHIV-Ebola) V920-016 Partnership for Research on Ebola Vaccination (PREVAC)
Exposure during pregnancy	Special warnings and precautions for use and the Fertility, pregnancy and lactation sections of the product information. <i>What you need to know before you receive ERVEBO</i> section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: WHO-sponsored trial (V920-EAP5): Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo
Exposure during lactation	Special warnings and precautions for use and the Fertility, pregnancy and lactation	Routine pharmacovigilance activities

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	sections of the product information. <i>What you need to know before you receive ERVEBO</i> section of the patient information.	Additional pharmacovigilance activities: WHO-sponsored trial (V920-EAP5): Compassionate ring vaccination study to evaluate the safety of the Ebola vaccine in the Democratic Republic of the Congo
Exposure in HIV-infected individuals	Special warnings and precautions for use section of the product information. <i>What you need to know before you receive ERVEBO</i> section of the patient information.	Routine pharmacovigilance activities Additional pharmacovigilance activities: V920-015 African Canadian Study of HIV-Infected Adults and a Vaccine for Ebola (ACHIV-Ebola)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD) because the product is not yet licensed in any country, hence the EBD will be the IBD. The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live attenuated) is a live recombinant replication-competent viral vaccine produced using Vero cells. The virus consists of a Vesicular Stomatitis Virus (VSV) backbone (Indiana strain) with a deletion of the VSV-G envelope glycoprotein replaced with the surface glycoprotein of the Zaire Ebolavirus (ZEBOV) Kikwit 1995 strain. The envelope glycoprotein is the immunogen that confers immunity against Ebolavirus. The vaccine virus is produced in Vero cells. The harvested virus from the cell-culture is purified and stabilized by resuspending in 10 mM Tris pH 7.2 and rice-derived recombinant human serum albumin 2.5 g/L.

The applicant declared that recombinant Vesicular Stomatitis Virus strain Indiana with a deletion of the VSV envelope glycoprotein replaced with the Zaire Ebola Virus Kikwit 1995 strain surface glycoprotein has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers the active substance recombinant Vesicular Stomatitis Virus strain Indiana with a deletion of the VSV envelope glycoprotein replaced with the Zaire Ebola Virus Kikwit 1995 strain surface glycoprotein included in Ervebo to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ervebo (Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, live)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and since it is to be approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ebola Virus Disease (EVD) is an acute systemic febrile syndrome caused by Ebola filovirus with case fatality ranging from 30% to 90% and an incubation period of 2 to 21 days. The disease-to-infection ratio is generally described as being 1:1 but some EVD asymptomatic and pauci-symptomatic infections are increasingly described. The highest case fatality has historically been observed with Zaire Ebola virus (70%), the virus causing the 2014 outbreak in West Africa.

The pathogenesis of EVD is characterized by an intense inflammatory process, impaired haemostasis and capillary leaks, with mortality resulting from septic shock and multi-organ system failure. Initial signs and symptoms are nonspecific (fever, headache, myalgia, fatigue) and may mimic other more common conditions such as malaria. After one week, haemorrhagic manifestations can appear in more than half of the patients. EVD progresses with gastrointestinal symptoms, internal and external bleeding, and in some cases, rash and neurologic involvement. The varying spectrum of Ebola virus disease severity, and the presence of asymptomatic and paucisymptomatic cases, is increasingly acknowledged.

Fruit bats, often hunted for food such as *Hypsignatus* genus, are considered the reservoir for Ebola and Marburg filoviruses. However, this could only be confirmed for Marburg and the precise reservoir for Ebola virus remains unknown. Close contact with infected animals in the rainforest, often used as 'bushmeat' such as antelope or monkeys, is a likely route of transmission. Twenty-five EVD outbreaks have been recorded so far. The largest outbreak before the 2014 outbreak was in Uganda in 2000 to 2001, with 425 cases. In more than half of outbreaks, the animal origin of the virus could not be shown.

Pregnant women face high mortality and a high risk of miscarriage and stillbirth.

Ebola virus disease (EVD) is caused by infection with a filovirus of the Ebolavirus genus which includes five distinct species. Zaire, Sudan, Bundibugyo and Taï Forest ebolaviruses occur in Africa and cause serious illness in humans. Reston ebolavirus occurs in the Philippines and only causes asymptomatic illness in human. The first three, Bundibugyo ebolavirus, Zaire ebolavirus, and Sudan ebolavirus have been associated with large outbreaks in Africa. The virus causing the 2014–2016 West African outbreak belongs to the Zaire ebolavirus species. Although the ebolavirus species associated with the current outbreak in the DRC is the same species that caused the earlier outbreak (Zaire ebolavirus), genetic differences between the viruses suggest the two outbreaks are not linked.

Ebola viruses are highly transmissible by direct contact of a healthy person's broken skin or mucous membranes with organs, blood or other bodily fluids (e.g. urine, saliva, sweat, faeces, vomit, breast milk, and semen) of living or dead infected persons, any soiled material (e.g. soiled clothing, bed linen, gloves, protective equipment and medical waste), or semen from men who recovered from EVD. Most cases are caused by human to human transmission. The risk of transmission from contaminated surfaces is low and can be reduced even further by appropriate cleaning and disinfection procedures.

The virus can persist in immunologically privileged sites such as semen, breast milk, ocular (eye) fluid, and spinal column fluid of recovered patients. The exact duration of persistence and the magnitude of risk of transmission through survivors is currently unknown, but some body fluids have tested positive by RT-PCR for longer than 9 months.

3.1.2. Available therapies and unmet medical need

No treatment or vaccine is currently authorised for Ebola virus disease in the EU, but several investigational vaccines and treatments based on blood, immunological or antiviral therapies are in clinical development or recommended for emergency use.

The additional most promising vaccine under development is the 2-dose Ad26-ZEBOV/MVA-BN-Filo heterologous vaccine regimen developed by Janssen. Two Ebola vaccines were authorised for national use only in Russia and China in 2017, but limited information is available on clinical data.

Regarding therapeutics, preliminary data from the ongoing PALM trial in DRC showed that RGN-EB3 and mAb114 seem more promising among four investigational agents (ZMapp, remdesivir, mAb114 and REGN-EB3). For details of other investigative products see section 2.1.5.

Early supportive care with rehydration and symptomatic treatment improves survival, however based on limited data available from 27 patients treated in US and EU hospital still almost 20% of them died.

Prevention of EVD is currently accomplished through education on avoidance of risk factors, quarantine of infected individuals and the use of personnel protective equipment (PPE).

Given the lack of specific treatment currently available and the fact that EVD is a highly infectious disease associated with a high mortality rate (25 to 90%), there is clearly an urgent unmet medical need.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicentre, cluster-randomized, open-label study comparing 1 dose ($\geq 2 \times 10^7$ PFU) of V920 administered in immediate (D0) vaccination (n=4539, 51 clusters) vs. V920 administered in delayed (D21) vaccination (n=4557, 47 clusters) in adults defined as contacts or contacts-of-contacts around a confirmed Ebola index case, as well as children ≥ 6 YOA enrolled in later stages of the trial. The trial was conducted in Guinea and Sierra Leone between March 2015 and January 2016 towards the end of the outbreak.

The objective of the trial was to assess the efficacy in the prevention of EVD caused by Ebola Zaire virus by comparing immediate versus delayed ring vaccination.

The ring vaccination strategy increased the possibility of the study to yield robust data on the efficacy of the vaccine despite the low and declining incidence of EVD by involving small pockets of high-risk individuals with high EVD incidence. It has also proven to be effective in outbreak management of infectious diseases with relatively low reproduction number (R_0 , i.e. the number of cases one case generates on average over the course of its infectious period, in an otherwise uninfected population), as is the case for Ebola Zaire (R_0 of 1.5-2.5, compared to R_0 of 2-5 for HIV and R_0 of 12-18 for measles).

The main evidence of immunogenicity submitted is derived from eight Phase 1 dose-finding studies, and from two Phase 2 and 3 trials conducted during the time of the 2014 to 2016 Ebola outbreak in at-risk populations in Liberia (V920-009) and Sierra Leone (V920-011) as well as in populations not at risk in US, Canada and Spain (V920-012). In all 3 trials, immune responses after a single nominal dose of 2×10^7 pfu V920 were measured up until Month 12 (V920-009 and V920-011) or Month 24 (V920-012) post-vaccination in terms of anti-GP antibodies (GP-ELISA) and neutralizing antibodies (PRNT) with validated assays.

3.2. Favourable effects

The primary analysis to estimate vaccine efficacy against laboratory-confirmed EVD among all vaccinated subjects in the immediate vaccination arm after 10 days from vaccination compared to all subjects who

were eligible and consented on the Day 0 visit in the delayed vaccination arm resulted in a vaccine efficacy estimate of 100% (unadjusted 95% CI: 63.5% to 100%; adjusted 95% CI: 14.4% to 100%). This VE estimate is based on 10 EVD cases (in 4 rings) identified prior to vaccination in 1,429 subjects of the delayed arm (46 rings) compared to 0 cases in 2,108 vaccinated subjects in the immediate arm (51 rings). The secondary analysis to estimate vaccine efficacy against laboratory-confirmed EVD among all CCCs in the immediate vaccination arm versus all CCCs in the delayed vaccination arm resulted in a vaccine efficacy estimate of 64.6% (95% CI: -44.2% to 91.3%) $p=0.3761$.

After vaccination, there were no EVD cases amongst the 5,837 vaccinated individuals in all 117 rings, 10 days or more post-vaccination, both randomized (immediate, delayed) and non-randomized, during the study period of 84 days. Analysis to assess vaccine efficacy against death from laboratory confirmed EVD supports the primary analysis.

The seroresponse rate defined as a 2-fold increase from baseline and ≥ 200 EU/mL for GP-ELISA (primary endpoint) in a non-endemic population of adults 18-65 years of age was 98.6% (95% CI: 97.4%-99.3%) at any time point and 92.1% (95% CI: 88.4%-94.9%) at Month 24. GP-ELISA GMT peaked at Day 28 post-vaccination with 1262 EU/mL (95% CI: 1168.9-1362.6) and declined by approximately 25% at Month 24 post-vaccination to 920.3 EU/mL (95% CI: 820.4-1032.3). PRNT GMT peaked at Month 18 post-vaccination with 276.9 (95% CI: 248.3-308.9) and remained stable through Month 24 post-vaccination (V920-012 trial conducted in US, Canada, EU).

Sustained but lower seroresponse rate and GMT were observed in endemic populations. The seroresponse rate defined as a 2-fold increase from baseline and ≥ 200 EU/mL for GP-ELISA (primary endpoint) in an endemic population of adults 18-65 YOA was 93.8% (95% CI: 91.1%-95.8.3%) at any time point and 80.1% (95% CI: 76.2%-83.7%) at Month 12. GP-ELISA GMT peaked at Day 28 post-vaccination with 994.7 EU/mL (95% CI: 915.0-1081.3) and declined by approximately 33% at Month 12 post-vaccination to 661.4 EU/mL (95% CI: 613.2-712.4). PRNT GMT peaked at Day 28 post-vaccination with 116.8 (95% CI: 106.0-128.8) and remained stable through Month 12 post-vaccination (V920-009 trial conducted in Liberia).

The immunogenicity data indicate a robust and sustainable immune response in healthy adults at risk and not at risk of infection through to two years post-vaccination. Overall, non-clinical primary pharmacodynamic studies provided adequate evidence that V920 induces robust immune responses upon vaccination with a single dose and provides protection after EBOV challenge in NHP.

3.3. Uncertainties and limitations about favourable effects

Uncertainties remain as to the actual level of protection, the duration of protection and the type of protection (pre- or post-exposure prophylaxis) given the methodological peculiarities of the ring vaccination design and the exceptional circumstances experienced during a declining Ebola epidemic.

Formally, from a statistical perspective the trial was not successful at interim but randomized enrolment was stopped thereafter. As the primary analysis is based on the interim data, the trial hence overall could not demonstrate a statistically significant VE. VE estimates may lack precision as they are based on few cases from a limited number of clusters and the time window for case ascertainment was short. Bias on various levels, including possible imbalance between arms with respect to detection, reporting and transmission control measures as well as selection bias at enrolment due to possible unblinding on a larger scale, cannot be excluded. The impact and direction of potential biases cannot be assessed. However, no cases of EVD were observed in any subject ≥ 10 days after vaccination, and the clear-cut outcome of the study somehow mitigate potential uncertainties. More data is expected during the post-authorisation phase also from the current ongoing outbreak in DRC where the vaccine was deployed.

The exact duration of protection by a single IM administration of Ervebo in humans is currently not known. The ring trial had only a study period of 84 days. Loss of protection in the longer term after vaccination was suggested by a NHP study. Given the gap of knowledge about specific mechanism of protection and protective titres, it is uncertain whether the duration of protection associated with V920 can be deduced from immunogenicity data only. Need for and timing of a booster dose is currently not known.

Considering the Ebola incubation time of up to 21 days (even if most infections become symptomatic in 8-10 days), ring vaccination by design might have included both pre-and post-exposure vaccination. It might well be that the VE data have been gathered in a mixed population of pre- or post-exposed individuals. The data thus might represent a combined pre-and post-exposure effect of the vaccine.

It is unknown from breakthrough cases whether the vaccine would prevent mortality/morbidity and/or viral persistence in sanctuary sites such as the eye or brain.

There is limited data to conclude on the use in pregnant women and in immunocompromised individuals.

There are no data on co-administration with other vaccines, hence co-administration is not recommended.

It is uncertain whether the vaccine would protect against genetic variants of the Zaire Ebolavirus as it is currently not known which epitopes are responsible for the immune responses. Also, within the same species of Zaire ebolavirus, genetic differences between viruses have been reported. Nevertheless, while the vaccine construct is based on the Zaire Kikwit strain, it was shown that V920 was effective against the Zaire Makona strain that circulated in West Africa in 2014-2016, and preliminary data suggest efficacy against the strain currently circulating in the DRC.

A correlate of protection is currently not known. The immunogenicity data indicate a sustainable humoral immune response induced by Ervebo through two years (V920-012 study). Antibodies measured by ELISA tend to decline slight to moderate, but continuously through two years. This effect is less visible in antibodies measured by PRNT. In lack of an immune correlate or of a biomarker for protection, sustained long-term efficacy cannot be directly inferred from the persisting antibody titres. Long-term immunogenicity and the need/optimal time point for a booster dose are currently unknown.

The evaluation of immunogenicity was based on Ebola-GP-specific IgG antibodies measured by ELISA and neutralizing antibodies by PRNT assay. No conclusive analysis of CMI responses after vaccination is currently available. See section 3.7.2 for uncertainties with respect to manufacturing process details.

3.4. Unfavourable effects

The safety of V920 was assessed based on data collected in 15.398 healthy adults receiving $\geq 2 \times 10^7$ pfu in 8 phase 1 studies and 4 phase 2/3 studies. The trials were conducted in different geographical regions (e.g., Africa only vs Europe/North America only) and under different circumstances (e.g., outbreak vs non-outbreak, community vs clinical settings), and used varying methods for data collection (e.g., phone contact with subjects vs in-person visits). A total of 234 children and adolescents 6 to <18 years of age were enrolled and received the clinical dose. Also, 536 (8.4%) of eligible, consented subjects were ≥ 65 years of age in the V920-010 trial. A total of 261 women were incidentally found to be pregnant after vaccination.

The most common injection-site adverse reactions were injection-site pain (70.3%), swelling (16.7%) and erythema (13.7%). The most common systemic adverse reactions reported following vaccination with V920 were headache (36.9%), pyrexia (34.3%), myalgia (32.5%), fatigue (18.5%), arthralgia (17.1%), nausea (8.0%), chills (6.3%), arthritis (3.7%), rash (3.6%), hyperhidrosis (3.2%), and abdominal pain (1.4%). In general, these reactions were reported within 7 days after vaccination, were mild to moderate in intensity, and had short duration (less than 1 week). Arthralgia was generally

reported in the first few days following vaccination, was mild to moderate in intensity, and resolved within one week after onset.

In the Phase I studies as well in the Phase II/III studies arthritis and arthralgia were recorded with a reporting rate of 15% to 50%. Partially these events were recorded up to 62 days or even left unresolved after the end of the trial.

Rash was characterized in a variety of ways including generalized rash, dermatitis, vesicular rash or cutaneous vasculitis. In a small number of subjects, the V920 vaccine virus was detected in rashes (described as dermatitis, vesicles or cutaneous vasculitis lesions) suggesting a virally mediated process post-vaccination. There was no evidence of systemic vasculitis.

Transient decreases in counts of lymphocytes, neutrophils and total white blood cells in the first 3 days following vaccination have been observed very commonly in Phase 1 studies. These events generally resolved after the first week post-vaccination.

3.5. Uncertainties and limitations about unfavourable effects

The trials were not designed or conducted by the various sponsors with the final objective of data integration among them. The integrated safety database consists of only serious adverse events (SAEs) data from 7 double-blinded studies (Phase 1 studies V920-001, V920-002, V920-003, V920-004, V920-005 phase 2/3 studies, V920-009, and V920-012). SAEs data across the randomized blinded trials were more uniformly collected and thus data integration was feasible.

The precise magnitude and duration of viremia and shedding remain unknown. Transmission of vaccine virus was not evaluated in clinical trials. A theoretical possibility of transmission of the vaccine virus through contacts of vaccinated persons exists. Therefore, a minimum 6-weeks period is currently recommended as the time required for vaccinees to avoid blood donation and contact with blood and bodily fluids as well as at risk individuals.

Safety in pregnant/breastfeeding women is not established. Some data is available but is not sufficient to draw conclusions; therefore, vaccination should be avoided during pregnancy and pregnancy should be avoided for 2 months after vaccination. More information should become available from the expanded access protocol in DRC. Nevertheless, considering the severity of EVD, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

The safety of Ervebo has not been assessed in severely immunocompromised individuals. In individuals with a defect in innate or adaptive immunity, the live-replicating vaccine could theoretically produce a more active or long-lasting infection with the vaccine virus, the outcome of which could be a severe illness. More data is expected post-authorisation from planned studies.

Vaccine virus RNA was found in blood, saliva and urine, synovial fluid (in 3 subjects who had arthritis TEAEs) and vesicles (n=4/10) of vaccinated adults, although at low incidence and low copy number in most adult subjects. Transmission through close personal contact is a theoretical possibility but is considered to be low risk because of the low magnitude of shedding. Transmission of vaccine virus was not evaluated in clinical trials. See section 3.7.2 for uncertainties with respect to manufacturing process details.

3.6. Effects Table

Table 22. Effects Table for Ervebo

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy against cEVD (primary endpoint)	Based on cases in vaccinees in the Immediate arm (N=2108 51 clusters]) vs cases in Delayed (control) arm ^a (1429 subjects [46 clusters]) ^b	N. of cEVD cases (N. clusters affected)	0(0)	10(4)	A statistically significant VE could not be demonstrated ^c . No clinical data on long term protection. No EVD developed in any vaccinees ≥10 days after vaccination.	Study V920-010
		100% (unadjusted 95% CI 63.5%; 100% - 95% CI adjusted for multiplicity: 14.4%; 100%) p-value (Fisher's exact test, 2-sided) 0.0471 ^c				
Vaccine effectiveness against cEVD (secondary endpoint, ITT)	Calculated in all CCCs in the immediate arm [N=4513 (51 clusters)] vs. all CCCs in the delayed arm [N=4529 (47 clusters)] ^d	N. of EVD cases (N. clusters affected)	10(5)	22(8)	The population for this analysis was pre-specified. The period for censoring the data (<10 days after randomisation) was not pre-specified.	
		64.6 % (95% CI) (-44.2; 91.3%) p-value ^c (Fisher's exact test, 2-sided): 0.3761				
Unfavourable Effects						
Arthralgia	mild to moderate in intensity	%	17.1	3.0	resolved within one week after onset	Study V920-005
Arthritis	mild to moderate in severity	%	3.7	0.0	median duration 2 days to 81.5 days, (including recurrent arthritis) with a maximum of 330 days	Study V920-012
Decreased white blood cell count ^e	Seen in the first 3 days following vaccination. Transient	%	≥10%	<10%	events generally resolved after the first week post-vaccination	Phase I trials V920-001 and V920-005

Abbreviations: cEVD: confirmed Ebolavirus Disease case; CCCs: contacts-of-contacts; ITT Intention-to-treat analysis; N.: number.

Notes:

a: All Eligible and Consented on Day 0 Visit

b:The populations of analysis and the period for censoring the data (<10 days after randomisation) were not pre-specified. Vaccine efficacy has been established in the period ≥ 10 to ≤ 31 days after vaccination.

c: Randomization was stopped after an interim analysis with a $p=0.0036$ that did not meet the pre-specified alpha level of 0.0027. Randomization was stopped because of the low probability of being able to recruit substantial numbers of additional rings. Confidence intervals and p-values adjusted using the pre-planned alpha-spending approach should be used. Hence, the significance level to be used is 0.0027 rather than 0.05

d: cEVD with onset 10-31 days after randomization

e: lymphocytes, neutrophils and total white blood cells.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The proposed indication for Ervebo is for active immunization of individuals 18 years of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.

The observed vaccine effect against EVD and EVD death is representing a true clinical benefit. The evidence for vaccine efficacy is adequate, based on the comprehensive analysis sets and the fact that none of the 5,837 vaccinated subjects developed EVD 10 days or more post-vaccination, regardless of the allocated groups. As EVD has an incubation time of 2-21 days (mainly 8-10 days), vaccination could occur during the incubation time and these EVD cases could be included in the primary efficacy analysis despite the 10-day censor period. Thus, the efficacy data may cover both pre-and post-exposure prophylactic effect of the vaccine. V920 induces robust immune responses upon vaccination with a single dose, and provides protection after EBOV challenge in NHP. Together with the demonstration of immunogenicity in human, these NC data suggest that Ab might be important in the prophylactic protection in humans. Since the viruses that cause EVD are located mainly in sub-Saharan Africa, the use of Ervebo within the European context is considered to be very specific, and is understood to be mainly aimed for health care workers deploying to an Ebola outbreak region (who would be vaccinated prior to embarking on such mission) or for ring vaccination around an 'imported' EVD case (where people at risk of being infected would need to be identified).

Vaccination was generally associated with a reactogenicity profile common to most vaccines. However, several forms of arthritis were commonly observed, most of which resolved within days or weeks of onset, but some became chronic (lasting up to 2 years following vaccination, the longest follow-up period) and it is currently unclear if or when they will resolve.

3.7.2. Balance of benefits and risks

The documented protective efficacy of Ervebo against EVD and EVD death is considered to be of high clinical benefit, but the exact magnitude and duration of vaccine-induced protection is currently still not fully known. Thus, it remains of utmost importance that vaccinees continue to adhere to Ebola control measures. The protection observed within a ring vaccination context in an outbreak region might also be less robust as compared to a blinded, placebo controlled trial, mostly because efficacy could only be evaluated in a short time window, therefore until new data is assessed it is important that the vaccine is considered for used in individuals at immediate risk of infection.

Based on the available safety data it can be concluded, that there is no safety concern related to the use of V920 in the target population (adults >18 YOA at risk of infection). The occurrence of chronic arthritis in a limited number of subjects was considered to be clinically relevant and the occurrence of mild to moderate reactogenicity was considered of limited clinical relevance. Only limited safety data were collected in pregnant women and immunocompromised individuals. This does not allow final conclusion on the safe use in this special populations.

The occurrence of binding and neutralizing antibodies against the Ebola Zaire GP-protein is considered to be relevant from an immunological point of view, but the clinical relevance in terms of magnitude and duration of protection is uncertain, as there is no immune correlate of protection. Nevertheless, the immunogenicity data indicate a sustained humoral immune response induced by Ervebo through two years post-vaccination.

No clinical data on long term protection are available.

Conditional marketing authorisation

Data on certain manufacturing process details are incomplete at time of opinion, specifically on the confirmation of the validated status of the active substance (AS) and finished product (FP) manufacturing process. In addition, comprehensive comparability data demonstrating that the commercial product manufactured at the Burgwedel site has not yet been completed to confirm the representativeness of the material used in the clinical trials. Additional AS and FP process validation/process performance qualification (PPQ) data and a comparability assessment will be provided post-approval. Furthermore, data are expected post-approval to: complete qualification of the master/working cell banks substrate used for production to include also tests for specified viruses; provide additional qualification data for the critical reagent used in the identity test (quality control release test for AS and FP) and introduce an additional in-process test for residual host cell protein, which will provide an additional control of impurities in the absence of a fully validated process.

As the above requested data on product manufacture are not available at the time of opinion, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the prevention of a life-threatening disease. Ebola Virus Disease (EVD) is an acute systemic febrile syndrome caused by Ebola filovirus with case fatality ranging from 30% to 90%. In addition, the product is to be used in emergency situations in response to public health threats duly recognised by the World Health Organisation. Currently an Ebola outbreak is ongoing in the Democratic Republic of Congo, which has been recognised by WHO as a PHEIC in August 2019, and Ervebo is being deployed in the region in the context of an expanded access protocol in collaboration with WHO.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. Studies are underway to complete the manufacturing process details. Detailed plans have been submitted in the dossier regarding scheduling of process validation data and the feasibility of completion of all proposed specific obligations has been assessed by the CHMP based upon the applicant's justification. Based on the applicant's plans and documentation, it is expected that data to fulfil all SOs will be submitted by end October 2020.
- Unmet medical needs will be addressed, as the data available indicate that Ervebo is highly efficacious in preventing EVD. There are no vaccines or therapeutics currently authorised for prevention or treatment of EVD.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The current data set indicate but do not permit a definitive conclusion that: the AS process is sufficiently validated to be capable of producing AS batches of

adequate and consistent quality; that the commercial product is fully comparable to the clinical batches used in the trials (produced at IDT Biologika and West Point); that the viral safety testing conducted on the master cell/ working cell substrates used for production is complete for two specified viruses and that a critical reagent used in the identity test has been fully qualified. Specific obligations to collect these data have been set accordingly. Since for biological products a combination of specifications and process control/validation is per definition deemed essential to guarantee product quality, it cannot be excluded that high variability of AS lots (due to insufficient process control) may result in differences in impurities or other properties or characteristics such as vaccine stability. However, additional routine testing (for two key specified impurities) in order to have an acceptable level of quality control of commercial product has been introduced and a test for a third key impurity, residual host cell protein is expected to be implemented shortly post-approval (specific obligation). With respect to viral safety testing of the cell banks substrates used for production, the applicant has provided reassurance on the viral safety of the cell bank system using a combination of specific tests and metagenomics analysis, however additional testing is required to complete the testing. Similarly, additional qualification data are required to complete the information on the critical reagent used for the identity assay to fully confirm the absence of any false-positive results.

Regarding vaccine potency however, any final product lots that comply with the currently proposed FP specifications, and that are formulated using AS lots that comply with the AS specifications, are expected to behave similarly in terms of potency as the clinical batches. Despite the potential risks described above with respect to manufacturing, the commercial process is identical to the clinical lot process (also with respect to scale) and as such, when executed in line with the described control strategy, the process is expected to yield AS of the same quality. All clinical lot material produced thus far has been shown to be of adequate and consistent quality. The current specifications (including potency) and acceptance limits proposed for the MAA are deemed appropriate and sufficiently justified (taking into account results from clinical batches). The additional data on the manufacturing process details of Ervebo are expected to be submitted by the end of October 2020. Based on all the above it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of EVD and the international context of the ongoing PHEIC, since the demonstrated benefits in the current emergency setting clearly outweigh the risks related to the limitations of the available data concerning manufacture of this product.

3.8. Conclusions

The overall B/R of Ervebo is positive provided that the conditions and obligations identified in the recommendation section are complied with.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ervebo is favourable in the following indication:

“Ervebo is indicated for active immunization of individuals 18 years of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus (see sections 4.2, 4.4 and 5.1). The use of Ervebo should be in accordance with official recommendations.”

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption is subject to annual review and in any case ceases to be valid on 31 July 2022. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 July 2022 at the latest, in line with the agreed plan for this transfer of testing. A progress report has to be included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional

This being a conditional marketing authorisation and pursuant to Article 14-a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
SO1: The MAH should provide additional data to confirm that the active substance (AS) process is properly validated. Process and batch data from at least 3 representative AS batches should be provided.	29 May 2020
SO2: The MAH should provide additional data to confirm that the finished product (FP) process is properly validated. Process and batch data from at least 3 representative FP batches should be provided.	30 Oct 2020
SO3: The MAH should provide comprehensive comparability data confirming that the commercial product manufactured at the Burgwedel site is representative of the material used in the clinical trials.	29 May 2020
SO4: The MAH should complete master cell banks (MCB)/working cell bank (WCB) qualification to include also tests for specified viruses.	30 Oct 2020
SO5: The MAH should provide additional qualification data for the critical reagent used in the identity test (quality control release test for AS and FP).	31 Jan 2020
SO6: The MAH should develop and introduce an active substance in-process control for total protein with appropriate acceptance criteria.	29 May 2020

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Recombinant Vesicular Stomatitis Virus strain Indiana with a deletion of the VSV envelope glycoprotein replaced with the Zaire Ebola Virus Kikwit 1995 strain surface glycoprotein is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.